

Multi-arm covariate-adaptive randomization

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Abstract Simultaneously investigating multiple treatments in a single study achieves considerable efficiency in contrast to the traditional two-arm trials. Balancing treatment allocation for influential covariates has become increasingly important in today's clinical trials. The multi-arm covariate-adaptive randomized clinical trial is one of the most powerful tools to incorporate covariate information and multiple treatments in a single study. Pocock and Simon's procedure has been extended to the multi-arm case. However, the theoretical properties of multi-arm covariate-adaptive randomization have remained largely elusive for decades. In this paper, we propose a general framework for multi-arm covariate-adaptive designs which also includes the two-arm case, and establish the corresponding theory under widely satisfied conditions. The theoretical results provide new insights into the balance properties of covariate-adaptive randomization procedures and make foundations for most existing statistical inferences under two-arm covariate-adaptive randomization. Furthermore, these open a door to study the theoretical properties of statistical inferences for clinical trials based on multi-arm covariate-adaptive randomization procedures.

Keywords multiple treatment, balancing covariate, clinical trial, marginal balance, Markov chain, Hu and Hu's general procedure, Pocock and Simon's procedure, stratified permuted block design

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1 Introduction

The multi-arm randomized clinical trial has been an important topic in some cases [15, 29, 38]. Especially, it is playing an increasingly significant role in epidemic diseases such as COVID-19 [3, 36], and cancers such as lung cancer [46] and glioblastoma [2]. To the best of our knowledge, clinical trials are expensively conducted [11, 28], whereas unacceptably few regimens can be put on the market. Furthermore, personalized medicine gains more and more popularity and thus leads to increasingly complex therapies. Hence, concerns have been raised among clinical trialists regarding how to efficiently and in less time find beneficial treatments. Simultaneously investigating multiple treatments in a single study achieves considerable efficiency in contrast to the traditional two-arm trials [32]. The multi-arm randomized clinical trial is one of the most powerful tools to incorporate multiple regimens in a single clinical trial.

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On the one hand, it dramatically reduces the required sample sizes compared with conducting several traditional two-arm randomized clinical trials separately for various involving regimens. On the other hand, fewer patients are required to receive the placebo, and then patients would be allocated to a promising treatment in greater probability. Therefore, multi-arm randomized clinical trials would attract more patient recruitment to the trial. There is a growing list of literature on multi-arm randomized clinical trials, such as development of new clinical trial procedures [5, 40, 42], applications in practice [27, 31], and discussion of its advantages [39, 41].

Among randomized clinical trials with multiple treatments, multi-arm covariate-adaptive randomization is preferred. It is well known that covariates play an essential role in clinical trials. Clinical trialists are often concerned about unbalanced treatment arms with respect to key covariates of interest. In the literature, covariate-adaptive randomization procedures are sometimes employed to balance important covariates [30]. The similarity of covariates between treatment groups enhances statistical efficiency and ensures convincing analysis [20]. Over the past several decades, scientists have identified many new biomarkers [1, 4, 13, 25, 34] that may link certain diseases in the fields of translational research (genomics, proteomics and metabolomics). Based on these biomarkers, we would like to develop personalized medicine algorithms that help patients to receive better treatment regimens based on their individual characteristics (which could be biomarkers or other covariates). To design a superior and efficient clinical study for personalized medicine, one should incorporate information on important biomarkers [15]. Therefore, balancing treatment allocation for influential covariates has become increasingly important in today's clinical trials. In a survey of 224 randomized clinical trials published in 2014 in leading medical journals, 183 (82%) have used the covariate-adaptive randomization [21]. Arguably, covariate-adaptive randomization gains more popularity at the design stage of a trial.

As pointed out in [15], classical covariate-adaptive designs have several drawbacks to incorporate many important biomarkers. For example, the stratified permuted block randomization [43] fails to achieve overall and marginal balances when a moderate sample size and a large number of covariates are involved. To address the potential problems of classical randomization schemes, Hu and Hu [19] developed a class of covariate-adaptive biased coin randomization procedures and studied its theoretical properties. However, the theoretical properties were induced under a strict condition (see [19, Condition (C) of Theorem 3.2]). Therefore, the properties are not suitable for most existing randomization schemes, especially Pocock and Simon's procedure, because of the limitation of the condition. More importantly, Hu and Hu's general covariate-adaptive randomization [19] is merely proposed in the two-arm case. Although Pocock and Simon [29] generalized the minimization method, which is one popular covariate-adaptive design for the multi-arm case, little knowledge on the theoretical properties is studied.

In this paper, we first develop a general family of multi-arm covariate-adaptive randomization procedures, which includes the two-arm case. Also, the proposed procedure includes some new designs and many existing designs with multiple treatments as special cases. We further establish a general theoretical foundation under widely satisfied conditions. In particular, we have theoretically proved that under the multi-arm Pocock and Simon's procedure, the marginal imbalances and overall imbalance are bounded in probability, but all the within-stratum imbalances increase with the rate \sqrt{n} as the sample size n increases. The theory provides some new insights into the theoretical properties of covariate-adaptive randomization procedures. The theory particularly provides critical conditions for general covariate-adaptive randomization procedures to achieve good within-stratum and marginal balances. As discussed in the concluding remarks (see Section 5), our theoretical results make foundations for most existing statistical inferences under two-arm covariate-adaptive randomization. Furthermore, these results also open a door to study the theoretical behavior of inferential methods (such as estimation and hypothesis test) of clinical trials based on multi-arm covariate-adaptive randomization procedures.

To study the theoretical properties under this general framework, one has the following main difficulties: (i) the correlation structure of within-stratum imbalances; (ii) the relationship among within-stratum and marginal imbalances under Pocock and Simon's procedure; (iii) the discreteness of the allocation function. In the literature, Taylor's expansion and martingale approximation are two common techniques for the study of the theoretical properties of adaptive designs with a continuous allocation function

[16, 17, 44]. Under Pocock and Simon’s procedure, to overcome the complex relationship among within-stratum and marginal imbalances, we have to approximate these imbalances using martingales by solving Poisson’s equation. To deal with the discreteness of the allocation function, we use the technique of “drift conditions” [26], which was developed for Markov chains on general state spaces.

The rest of this paper is organized as follows. The general framework of the multi-arm randomization procedure is described in Section 2 and the theoretical results are given in Section 3. In Section 4, we further conduct several simulation studies to corroborate the theoretical properties proposed in Section 3, and compare various randomization schemes in different scenarios. Some concluding remarks are in Section 5. The proofs of the theorems can be found in the appendix.

2 The general multi-arm covariate-adaptive randomization procedure

We consider the same setting as that of [29] with T ($T \geq 2$) treatments. Consider I covariates and m_i levels for the i -th covariate, resulting in $m = \prod_{i=1}^I m_i$ strata. Let T_j be the assignment of the j -th patient and $j = 1, \dots, n$. Let Z_j indicate the covariate profile of the j -th patient, i.e., $Z_j = (k_1, \dots, k_I)$ if his or her i -th covariate is at level k_i ($1 \leq i \leq I$) and $1 \leq k_i \leq m_i$. For convenience, we use (k_1, \dots, k_I) to denote the stratum formed by patients who possess the same covariate profile (k_1, \dots, k_I) , and use $(i; k_i)$ to denote the margin formed by patients whose i -th covariate is at level k_i .

The new procedure is defined as follows:

- (1) The first patient is assigned to the treatment t ($t = 1, \dots, T$) with probability $p = 1/T$.
- (2) Suppose that $j - 1$ patients have been assigned to treatments ($1 < j \leq n$), and the j -th patient falls within the stratum (k_1^*, \dots, k_I^*) .
- (3) (Differences for each treatment) For the first $j - 1$ patients, let $N_{j-1}^{(t)}$, $N_{j-1}^{(t)}(i; k_i^*)$ and $N_{j-1}^{(t)}(k_1^*, \dots, k_I^*)$ be the numbers of patients in the treatment t in total, on the margin $(i; k_i^*)$ and within the stratum (k_1^*, \dots, k_I^*) , respectively. We define

$$\bar{N}_{j-1} = \frac{1}{T} \sum_{t'=1}^T N_{j-1}^{(t')}$$

as the average number of patients over treatments. Furthermore, the marginal average number of patients $\bar{N}_{n-1}(i; k_i^*)$ and the within-stratum average number of patients $\bar{N}_{j-1}(k_1^*, \dots, k_I^*)$ are defined in the similar way. Then let

$$\begin{aligned} D_{j-1}^{(t)} &= N_{j-1}^{(t)} - \bar{N}_{j-1}, \\ D_{j-1}^{(t)}(i; k_i^*) &= N_{j-1}^{(t)}(i; k_i^*) - \bar{N}_{j-1}(i; k_i^*), \\ D_{j-1}^{(t)}(k_1^*, \dots, k_I^*) &= N_{j-1}^{(t)}(k_1^*, \dots, k_I^*) - \bar{N}_{j-1}(k_1^*, \dots, k_I^*) \end{aligned}$$

be the differences for the treatment t , which are used to measure the imbalances at the overall, marginal, and within-stratum levels, respectively.

- (4) If the j -th patient is assigned to the treatment t ($t = 1, \dots, T$), then
 - $N_{j-1}^{(t)}$, $N_{j-1}^{(t)}(i; k_i^*)$ and $N_{j-1}^{(t)}(k_1^*, \dots, k_I^*)$ would increase by 1, while others remain unchanged;
 - the potential differences at the corresponding levels would be

$$\begin{aligned} D_{j,t}^{(t')} &= D_{j-1}^{(t')} + \mathbb{I}_{(t'=t)} - \frac{1}{T}, \\ D_{j,t}^{(t')}(i; k_i^*) &= D_{j-1}^{(t')}(i; k_i^*) + \mathbb{I}_{(t'=t)} - \frac{1}{T}, \\ D_{j,t}^{(t')}(k_1^*, \dots, k_I^*) &= D_{j-1}^{(t')}(k_1^*, \dots, k_I^*) + \mathbb{I}_{(t'=t)} - \frac{1}{T}, \end{aligned}$$

where $t' = 1, \dots, T$.

(5) (Measurement) Define an imbalance measurement $\text{Imb}_j^{(t)}$ by

$$\begin{aligned} \text{Imb}_j^{(t)} = & w_o \left\{ \sum_{t'=1}^T (D_{j,t}^{(t')})^2 \right\} + \sum_{i=1}^I w_{m,i} \left\{ \sum_{t'=1}^T (D_{j,t}^{(t')}(i; k_i^*))^2 \right\} \\ & + w_s \left\{ \sum_{t'=1}^T (D_{j,t}^{(t')}(k_1^*, \dots, k_I^*))^2 \right\}, \end{aligned} \tag{2.1}$$

which is the weighted imbalance; it would be obtained if the j -th patient is assigned to the treatment t . w_o , $w_{m,i}$ ($i = 1, \dots, I$) and w_s are non-negative weights placed overall, within a covariate margin and a stratum cell, respectively. Without loss of generality, we assume

$$w_o + \sum_{i=1}^I w_{m,i} + w_s = 1.$$

(6) (Probability generator) We define the allocation probabilities following [29]. Suppose that the $\text{Imb}_j^{((t))}$ is the t -th order statistic that is the t -th smallest value of the random samples $\text{Imb}_j^{(1)}, \dots, \text{Imb}_j^{(T)}$. One thus can rank the treatments according to the values of $\text{Imb}_j^{(t)}$ ($t = 1, \dots, T$) in a non-decreasing order so that

$$\text{Imb}_j^{((1))} \leq \text{Imb}_j^{((2))} \leq \dots \leq \text{Imb}_j^{((T))}.$$

In the case of ties, a random ordering can be determined. Then conditional on the assignments of the first $j - 1$ patients and the covariates' profiles of the first j patients, assign the j -th patient to the treatment t with the probability

$$P(T_j = t \mid \mathcal{F}_{j-1}, Z_j = (k_1^*, \dots, k_I^*)) = p_{j,t}, \tag{2.2}$$

where $\mathcal{F}_j = \sigma(Z_1, \dots, Z_j; T_1, \dots, T_j)$, which is the history σ -field generated by the covariates Z_1, \dots, Z_j and the assignments T_1, \dots, T_j . Here, $p_{j,t}$ is a function with respect to the ranking of $\text{Imb}_j^{(t)}$ among the random samples $\text{Imb}_j^{(t')}$ ($t' = 1, \dots, T$), and

$$p_{j,t} = p_{t'}, \quad \text{if } \text{Imb}_j^{(t)} = \text{Imb}_j^{((t'))}, \quad t' = 1, \dots, T, \tag{2.3}$$

where $p_1 \geq p_2 \geq \dots \geq p_T$ are T ordered positive constants with $\sum_{t'=1}^T p_{t'} = 1$.

The imbalance measurement defined in (2.1) is a critical quantity. For all t and t' ($t', t = 1, \dots, T$), using the basic equation $(x + 1)^2 - x^2 = 2x + 1$, we can simplify the difference of $\text{Imb}_j^{(t)}$ and $\text{Imb}_j^{(t')}$ as

$$\begin{aligned} \text{Imb}_j^{(t)} - \text{Imb}_j^{(t')} = & 2 \left\{ w_o D_{j-1}^{(t)} + \sum_{i=1}^I w_{m,i} D_{j-1}^{(t)}(i; k_i^*) + w_s D_{j-1}^{(t)}(k_1^*, \dots, k_I^*) \right\} \\ & - 2 \left\{ w_o D_{j-1}^{(t')} + \sum_{i=1}^I w_{m,i} D_{j-1}^{(t')}(i; k_i^*) + w_s D_{j-1}^{(t')}(k_1^*, \dots, k_I^*) \right\} \\ =: & 2 \times [\Lambda_{j-1}^{(t)}(k_1^*, \dots, k_I^*) - \Lambda_{j-1}^{(t')}(k_1^*, \dots, k_I^*)]. \end{aligned} \tag{2.4}$$

Accordingly, the order of $\{\text{Imb}_j^{(t')}, t' = 1, \dots, T\}$ is the same as that of $\{\Lambda_{j-1}^{(t')}(k_1^*, \dots, k_I^*), t' = 1, \dots, T\}$ for the stratum (k_1^*, \dots, k_I^*) . Therefore, the allocation probability $p_{j,t}$ is determined by the values of $\Lambda_{j-1}^{(t')}(k_1^*, \dots, k_I^*)$ ($t' = 1, \dots, T$), which is a weighted average of current imbalances for the treatment t' at different levels.

Remark 2.1. This general framework includes most covariate-adaptive randomization procedures in the literature as special cases. For example, when the marginal imbalances are only considered, i.e., $w_o = w_s = 0$, it reduces to Pocock and Simon's procedure; when $w_{m,i} = w_o = 0$, it reduces to the multi-arm stratified randomization. Also, if only two treatments are considered ($T = 2$), we obtain the family of covariate-adaptive randomization studied in [19]. We hope that the general framework is flexible in defining applicable randomization procedures with good properties. The theoretical results are established under widely satisfied conditions so that they can apply to all the cases.

3 Theoretical properties of the general multi-arm covariate-adaptive randomization

We now investigate the asymptotic properties of the general multi-arm covariate-adaptive randomization. For the first n patients, let

$$\mathbf{D}_n = [D_n^{(t)}(k_1, \dots, k_I) : 1 \leq t \leq T; 1 \leq k_i \leq m_i, 1 \leq i \leq I]$$

be an array of dimension $T \times m_1 \times \dots \times m_I$, which stores the current imbalances in all the strata for each treatment. Also, assume that the covariates Z_1, Z_2, \dots are independently and identically distributed. Since $Z_n = (k_1, \dots, k_I)$ can take $m = \prod_{i=1}^I m_i$ different values, it in fact follows an m -dimensional multinomial distribution with parameter $\mathbf{p} = (p(k_1, \dots, k_I), \forall 1 \leq k_i \leq m_i, 1 \leq i \leq I)$, with each element being the probability that a patient falls within the corresponding stratum (k_1, \dots, k_I) . Obviously, $p(k_1, \dots, k_I) \geq 0$ and $\sum_{k_1, \dots, k_I} p(k_1, \dots, k_I) = 1$. Notice that

$$P(D_n^{(t)}(k_1, \dots, k_I) = D_1^{(t)}(k_1, \dots, k_I), t = 1, \dots, T, \forall n) = 1, \quad \text{if } p(k_1, \dots, k_I) = 0.$$

Therefore, the stratum (k_1, \dots, k_I) with $p(k_1, \dots, k_I) = 0$ can be ignored. Hence without loss of generality, we assume $p(k_1, \dots, k_I) > 0$ for any stratum (k_1, \dots, k_I) .

Our purpose is to study the properties of \mathbf{D}_n . Besides \mathbf{D}_n , we also consider the weighted average of the imbalances for each treatment $\Lambda_n^{(t)}(k_1, \dots, k_I)$ as in (2.4). Let

$$\Lambda_n = [\Lambda_n^{(t)}(k_1, \dots, k_I) : 1 \leq t \leq T; 1 \leq k_i \leq m_i, 1 \leq i \leq I].$$

The allocation probability $p_{n,t}$ ($t = 1, \dots, T$) in (2.2) is a function of Λ_{n-1} . Rather than explore the properties of \mathbf{D}_n directly, we firstly work on the properties of Λ_n . Then by investigating the relationship between \mathbf{D}_n and Λ_n , we further investigate the properties of \mathbf{D}_n . It is obvious that

$$\Lambda_n = \mathbf{L}(\mathbf{D}_n) : \mathbf{D}_n \rightarrow \Lambda_n$$

is a linear transformation of \mathbf{D}_n . The following proposition gives the relationship between \mathbf{D}_n and Λ_n and tells us that both $(\mathbf{D}_n)_{n \geq 1}$ and $(\Lambda_n)_{n \geq 1}$ are Markov chains.

Proposition 3.1. (i) If $w_s > 0$, then $\Lambda_n = \mathbf{L}(\mathbf{D}_n)$ is a one-to-one linear map. If $w_{m,i} + w_s > 0$, then $D_n^{(t)}(i; k_i) = D_{i;k_i}^{(t)}(\Lambda_n)$ is a linear transformation of Λ_n for any $t = 1, \dots, T$. For any cases, $D_n^{(t)} = D^{(t)}(\Lambda_n)$ is a linear transformation of Λ_n for any $t = 1, \dots, T$.

(ii) $(\mathbf{D}_n)_{n \geq 1}$ is an irreducible Markov chain on the space $\mathbb{R}^{T \times m}$ with period T . For any permutations $\Pi(1), \dots, \Pi(T)$ of $1, \dots, T$, the transition probabilities of

$$(D_n^{(\Pi(1))}(\mathbf{k}), \dots, D_n^{(\Pi(T))}(\mathbf{k}) : 1 \leq k_i \leq m_i, 1 \leq i \leq I)_{n \geq 1}$$

are the same.

(iii) $(\Lambda_n)_{n \geq 1}$ is an irreducible Markov chain on the space $\mathbf{L}(\mathbb{R}^{T \times m})$ with period T . For any permutations $\Pi(1), \dots, \Pi(T)$ of $1, \dots, T$, the transition probabilities of

$$(\Lambda_n^{(\Pi(1))}(\mathbf{k}), \dots, \Lambda_n^{(\Pi(T))}(\mathbf{k}) : 1 \leq k_i \leq m_i, 1 \leq i \leq I)_{n \geq 1}$$

are the same.

Now we give the main results of the general multi-arm covariate-adaptive randomization.

Theorem 3.2. Consider I covariates and m_i levels for the i -th covariate, where $I \geq 1$, $1 \leq i \leq I$ and $m_i > 1$. w_o , w_s and $w_{m,i}$ ($i = 1, \dots, I$) are non-negative with

$$w_o + \sum_{i=1}^I w_{m,i} + w_s = 1.$$

Assume that $p_1 \geq \dots \geq p_T$ are non-negative constants with $\sum_{t=1}^T p_t = 1$ and $p_1 > p_T > 0$. Then $(\mathbf{A}_n)_{n \geq 1}$ is a positive recurrent Markov chain with period T on $\mathbf{L}(\mathbb{R}^{T \times m})$ and $\mathbb{E}\|\mathbf{A}_n\|^r = O(1)$ for any $r > 0$. In particular,

(i) if $w_s > 0$, then $(\mathbf{D}_n)_{n \geq 1}$ is a positive recurrent Markov chain with period T on $\mathbb{R}^{T \times m}$; $\mathbb{E}\|\mathbf{D}_n\|^r = O(1)$ for any $r > 0$;

(ii) if $w_s + w_{m,i} > 0$, then $D_n^{(t)}(i; k_i) = O(1)$ in probability and $\mathbb{E}|D_n^{(t)}(i; k_i)|^r = O(1)$ for any $r > 0$ and $t = 1, \dots, T$; furthermore, if $w_s = 0$, then $(D_n^{(t)}(i; k_i) : w_{m,i} \neq 0, 1 \leq t \leq T; 1 \leq k_i \leq m_i, 1 \leq i \leq I)_{n \geq 1}$ is a positive recurrent Markov chain with period T ;

(iii) for any cases, $D_n^{(t)} = O(1)$ in probability and $\mathbb{E}|D_n^{(t)}|^r = O(1)$ for any $r > 0$ and $t = 1, \dots, T$; furthermore, if $w_{m,i} = w_s = 0$ ($i = 1, \dots, I$), then $(D_n^{(t)} : t = 1, \dots, T)_{n \geq 1}$ is a positive recurrent Markov chain with period T .

The next theorem tells us that the within-stratum imbalances $|D_n^{(t)}(k_1, \dots, k_I)|$ ($t = 1, \dots, T$) either are bounded in probability or increase with the rate \sqrt{n} as the sample size increases.

Theorem 3.3. Under the conditions in Theorem 3.2, we have the following results:

(iv) there exist non-negative constants $\sigma^{(t)}(k_1, \dots, k_I)$ such that

$$\mathbb{E}(D_n^{(t)}(k_1, \dots, k_I))^2 = n(\sigma^{(t)}(k_1, \dots, k_I))^2 + O(\sqrt{n}\sigma^{(t)}(k_1, \dots, k_I)), \quad (3.1)$$

$$\frac{D_n^{(t)}(k_1, \dots, k_I)}{\sqrt{n}} \xrightarrow{D} N(0, (\sigma^{(t)}(k_1, \dots, k_I))^2) \quad (3.2)$$

and

$$\lim_{n \rightarrow \infty} \mathbb{E} \left| \frac{D_n^{(t)}(k_1, \dots, k_I)}{\sqrt{n}} \right|^r = (\sigma^{(t)}(k_1, \dots, k_I))^r \mathbb{E}|N(0, 1)|^r \quad (3.3)$$

for all strata (k_1, \dots, k_I) s, $r > 0$ and $t = 1, \dots, T$, where $N(0, 1)$ is a standard normal random variable;

(v) for any fixed stratum (k_1, \dots, k_I) , if $D_n^{(t)}(k_1, \dots, k_I) = o(\sqrt{n})$ in probability, then $D_n^{(t)}(k_1, \dots, k_I) = O(1)$ in probability for any $t = 1, \dots, T$;

(vi) if $D_n^{(t)}(k_1, \dots, k_I) = o(\sqrt{n})$ in probability for one stratum (k_1, \dots, k_I) , then $w_s \neq 0$; in other words, if $w_s = 0$, then for all strata (k_1, \dots, k_I) ,

$$\lim_{n \rightarrow \infty} \frac{\mathbb{E}(D_n^{(t)}(k_1, \dots, k_I))^2}{n} = (\sigma^{(t)}(k_1, \dots, k_I))^2 > 0, \quad \forall t = 1, \dots, T.$$

Remark 3.4. We do not have a close form of the asymptotic standard deviation $\sigma^{(t)}(k_1, \dots, k_I)$. However, simulation studies show that the biased coin probabilities and weights (especially w_s) are critical to $\sigma^{(t)}(k_1, \dots, k_I)$ ($t = 1, \dots, T$), $1 \leq k_i \leq m_i$ ($i = 1, \dots, I$): (i) The asymptotic variance of $D_n^{(t)}(k_1, \dots, k_I)/\sqrt{n}$ is maximized under complete randomization with $w_o = w_s = w_{m,i} = 0$ ($i = 1, \dots, I$). (ii) Large biased coin probability p_1 reduces $\sigma^{(t)}(k_1, \dots, k_I)$ for the within-stratum imbalances. (iii) If we do not choose large enough values of w_s , larger values of biased coin probability p_1 are recommended to reduce the asymptotic standard deviation $\sigma^{(t)}(k_1, \dots, k_I)$. Similarly, if the biased coin probability is near 0.5, large values of w_s are suggested to achieve a small asymptotic standard deviation $\sigma^{(t)}(k_1, \dots, k_I)$.

The main conclusions of Theorems 3.2 and 3.3 can be summarized in the following corollary which indicates that the condition $w_s > 0$ is critical to ensure that $(\mathbf{D}_n)_{n \geq 1}$ is positive recurrent.

Corollary 3.5. The following statements are equivalent:

- (i) $(\mathbf{D}_n)_{n \geq 1}$ is a positive recurrent Markov chain;
- (ii) $\mathbf{D}_n = O(1)$ in probability;
- (iii) $\mathbb{E}\|\mathbf{D}_n\|^r = O(1)$ for all $r > 0$;
- (iv) $D_n^{(t)}(k_1, \dots, k_I) = o(\sqrt{n})$ in probability for at least one stratum (k_1, \dots, k_I) for any $t = 1, \dots, T$;
- (v) $w_s > 0$.

The next theorem tells us that the marginal procedures will not provide good balances with respect to the margin if one does not consider the margin in the imbalance measure for defining the allocation probability (2.2).

Theorem 3.6. *Suppose that the conditions in Theorem 3.2 are satisfied. If $w_s + w_{m,i} = 0$, then*

$$\lim_{n \rightarrow \infty} \frac{E[D_n^{(t)}(i; k_i)]^2}{n} > 0 \quad \text{for all } k_i = 1, \dots, m_i \text{ and } t = 1, \dots, T.$$

Remark 3.7. By Theorems 3.2, 3.3 and 3.6, the conditions $w_s > 0$ and $w_s + w_{m,i} > 0$ ($i = 1, \dots, I$) are critical to ensure that the within-stratum $D_n^{(t)}(k_1, \dots, k_I) = O(1)$ and the marginal imbalances $D_n^{(t)}(i; k_i) = O(1)$ in probability, respectively. However, we have not discussed the selection of these weights in practice. Here are some suggestions based on the results of this paper: (i) Always choose $w_s > 0$. (ii) When the sample size is relatively large and the total number of strata is relatively small, there are enough patients in each stratum. In these cases, the balance within each stratum is important, and w_s plays an important role; we may choose a relatively large w_s . For example, we may use $w_s = 1/2$ in these situations. (iii) When the number of covariates (I) is increasing and the number of strata is relatively large, we may select weights according to the number of covariates (I) and the importance of each covariate. For example, we may select $w_s = w_{m,i} = (I+1)^{-1}$ or $w_s = (I+1)^{-1}$ and $w_{m,i}$ according to the importance of the i -th covariate ($i = 1, \dots, I$). Note that putting too much emphasis on the within-stratum imbalances results in relatively significant increases in the overall and marginal imbalances. Consequently, a relatively small value of w_s is recommended if the primary goal of randomization is not to achieve the within-stratum imbalance, in the case of a small sample size compared with the number of strata. (iv) Large weights lead to more well-balanced performances at the corresponding levels. Thus, if a covariate is deemed essential, more weights can be shifted towards the within-stratum and marginal imbalances of the covariate.

When $w_s = 0$, the design reduces to the marginal procedure which includes Pocock and Simon's procedure [29] as a special case. Based on Theorems 3.2 and 3.3, we conclude the asymptotic properties for Pocock and Simon's procedure.

Corollary 3.8. *For Pocock and Simon's procedure ($w_o = w_s = 0$), then we have the following results:*

(i) *All the within-stratum imbalances increase with the rate \sqrt{n} as the sample size increases, and also $D_n^{(t)}(k_1, \dots, k_I)/\sqrt{n}$ is asymptotically normally distributed with a positive variance $(\sigma^{(t)}(k_1, \dots, k_I))^2$.*

(ii) *When $w_{m,i} > 0$, the corresponding marginal imbalance (the i -th covariate) and the overall imbalance are bounded in probability, i.e., $D_n^{(t)}(i; k_i) = O(1)$ and $D_n^{(t)} = O(1)$ in probability for any $t = 1, \dots, T$. Furthermore, the collection of all the marginal imbalances*

$$[D_n^{(t)}(i; k_i) : 1 \leq t \leq T, 1 \leq k_i \leq m_i, 1 \leq i \leq I]_{n \geq 1}$$

is a positive recurrent Markov chain with period T .

(iii) *When $w_{m,i} = 0$, the corresponding marginal imbalance increases with the rate \sqrt{n} , i.e., $D_n^{(t)}(i; k_i) = O_p(\sqrt{n})$ for any $t = 1, \dots, T$.*

Remark 3.9. The theoretical result (i) has been obtained in [19] under very strict conditions of the weights w_s and $w_{m,i}$ ($i = 1, \dots, I$) when $T = 2$. The condition (C) in [19, Theorem 3.2] for the general case is very restrictive and usually not satisfied in practice. When the number of strata is large, this condition can be satisfied only when w_s is very close to 1 and the design reduces to the stratified randomization. Both [19, Theorem 3.1] for the special case of 2×2 strata and [19, Theorem 3.2] for the general case of many strata do not apply to Pocock and Simon's procedure [29] (with $w_s = 0$) and the design with equal weights $w_o, w_{m,i}$ and w_s . Our theorems eliminate Hu and Hu's condition (C) [19] so that they can apply to most covariate-adaptive randomization procedures, in particular the family of Hu and Hu's general covariate-adaptive randomization. Then we conclude the main theorems when $T = 2$ as follows.

Let D_n be the difference between the numbers of patients assigned to the treatments 1 and 2. $D_n(i; k_i)$ and $D_n(k_1, \dots, k_I)$ are defined in the similar way. Consider I covariates and m_i levels for the i -th covariate, where $I \geq 1, 1 \leq i \leq I$ and $m_i > 1$. w_o, w_s and $w_{m,i}$ ($i = 1, \dots, I$) are non-negative with

$$w_o + \sum_{i=1}^I w_{m,i} + w_s = 1.$$

Then the main results for the general family of two-arm covariate-adaptive randomization are as follows:

- (i) if $w_s > 0$, then $(\mathbf{D}_n)_{n \geq 1}$ is a positive recurrent Markov chain with period 2 on \mathbb{Z}^m , and $E\|\mathbf{D}_n\|^r = O(1)$ for any $r > 0$;
- (ii) if $w_s + w_{m,i} > 0$, then $D_n(i; k_i) = O(1)$ in probability and $E|D_n(i; k_i)|^r = O(1)$; furthermore, if $w_s = 0$, then the collection of all the marginal imbalances $((D_n(i; k_i) : w_{m,i} \neq 0, k_i = 1, \dots, m_i, i = 1, \dots, I))_{n \geq 1}$ is a positive recurrent Markov chain;
- (iii) for any case $D_n = O(1)$ in probability and $E|D_n|^r = O(1)$ for any $r > 0$; furthermore, if $w_s = w_{m,1} = \dots = w_{m,I} = 0$, then $(\mathbf{D}_n)_{n \geq 1}$ is a positive recurrent Markov chain;
- (iv) if $w_s = 0$, then for all strata (k_1, \dots, k_I) ,

$$\lim_{n \rightarrow \infty} \frac{ED_n^2(k_1, \dots, k_I)}{n} > 0;$$

- (v) if $w_s + w_{m,i} = 0$, then

$$\lim_{n \rightarrow \infty} \frac{E[D_n^2(i; k_i)]}{n} > 0 \quad \text{for all } k_i = 1, \dots, m_i.$$

As in [19], to prove Theorem 3.2, we use the technique of “drift conditions” [26], which was developed for Markov chains on general state spaces. Instead of considering \mathbf{D}_n directly as in [19], we have to consider $\mathbf{\Lambda}_n$ in this paper. In order to prove the positive recurrence of $(\mathbf{\Lambda}_n)_{n \geq 1}$, we need to find a test function $V : \mathbf{L}(\mathbb{R}^{T \times m}) \rightarrow \mathbb{R}^+$, a bounded test set \mathcal{C} on $\mathbf{L}(\mathbb{R}^{T \times m})$ and a positive constant b such that

$$\Delta_\lambda V(\mathbf{\Lambda}) := \sum_{\mathbf{\Lambda}' \in \mathbf{L}(\mathbb{R}^{T \times m})} P_\lambda(\mathbf{\Lambda}, \mathbf{\Lambda}')V(\mathbf{\Lambda}') - V(\mathbf{\Lambda}) \tag{3.4}$$

satisfies the following condition:

$$\Delta_\lambda V(\mathbf{\Lambda}) \leq -1 + b\mathbb{I}_{\mathbf{\Lambda} \in \mathcal{C}}, \tag{3.5}$$

where $P_\lambda(\mathbf{\Lambda}, \mathbf{\Lambda}')$ is the transition probability from $\mathbf{\Lambda}$ to $\mathbf{\Lambda}'$ on the state space $\mathbf{L}(\mathbb{R}^{T \times m})$ of the chain $(\mathbf{\Lambda}_n)_{n \geq 1}$, and $\mathbb{I}_{\mathbf{\Lambda} \in \mathcal{C}}$ is a function with the value 1 if $\mathbf{\Lambda}$ is in \mathcal{C} , and 0 if not. V is often a norm-like function on $\mathbf{L}(\mathbb{R}^{T \times m})$. For considering the convergence of moments of the Markov chain, we also find the drift condition of $\Delta_\lambda V^r(\mathbf{\Lambda})$. The test function V is the key component in the proofs. We have to choose a good V such that it is a norm-like function and the drift $\Delta_\lambda V$ is also very close to the norm of $\mathbf{\Lambda}$, so that the drift condition is satisfied without any additional condition on the weights w_o , w_s , and $w_{m,i}$.

When $w_s = 0$ (Pocock and Simon’s procedure), the within-stratum imbalance $D_n^{(t)}(k_1, \dots, k_I)$ is not considered in the allocation procedure. We need to introduce a new technique (Poisson’s equation) to deal with the complicated structures of the within-stratum imbalances and marginal imbalances. In fact, we approximate $D_n^{(t)}(k_1, \dots, k_I)$ as a martingale plus a function of $\mathbf{\Lambda}_n$ by solving Poisson’s equation in the proof of Theorem 3.3. We prove that this martingale is a constant when the asymptotic variance $(\sigma^{(t)}(k_1, \dots, k_I))^2$ is zero so that $D_n^{(t)}(k_1, \dots, k_I)$ is a function of $\mathbf{\Lambda}_n$, which leads to a contradiction when $w_s = 0$. All the proofs are stated in the appendix.

4 Simulation studies

This section presents three simulation studies to explore the theoretical results and evaluate the performances under various covariate-adaptive randomization designs in achieving general balances. We compare the multi-arm general covariate-adaptive randomization with Pocock and Simon’s procedure, and the stratified permuted block randomization [43]. For clarity, we choose the weighted squares of the marginal imbalances for Pocock and Simon’s procedure [29] and consider the three-arm case hereafter. First, we simulate a case of 2×2 strata with a relatively large sample size to verify the asymptotic behavior of imbalances, which is stated in Section 3. Considering the case where the number of strata becomes large, whereas the number of patients is relatively small, we further conduct a study to compare different randomization procedures’ performances. To put the multi-arm general covariate-adaptive randomization into a wide application, we thus mimic a real-world example from [7]. Replication of 10^4 is used throughout the following simulations.

4.1 The case of 2×2 strata

In designing covariate-adaptive randomized clinical trials, we aim to ensure that the imbalances at the corresponding levels (overall, marginal and within-stratum) are bounded in probability. If the imbalances at all the three levels are bounded in probability, it leads to a well-balanced randomized clinical trial. The parameters are specified as follows:

- the multinomial probability: $(p(1, 1), p(1, 2), p(2, 1), p(2, 2)) = (0.1, 0.2, 0.3, 0.4)$;
- the sample size: the sample size n traverses from 200 to 2,000 with increment 300;
- the the allocation probability of the probability generator: $p_1 = 0.75, p_2 = 0.20$ and $p_3 = 0.05$ for the general procedure and Pocock and Simon’s procedure;
- the weights: $(w_o, w_s, w_{m,1}, w_{m,2}) = (0.3, 0.5, 0.1, 0.1)$ for the general procedure, while $(w_o, w_s, w_{m,1}, w_{m,2}) = (0, 0, 0.5, 0.5)$ for the Pocock and Simon’s procedure;
- the block size: the block size is set to be 6.

The standard deviations of imbalances at different levels under various randomization procedures are represented in Figure 1. Since the specified imbalances among different treatments have the same properties, we only illustrate the results for the treatment 1, i.e., the standard deviations of $D_n^{(1)}(\cdot)$. For simplicity, only the standard deviations at the overall levels, two of the within-stratum levels (1, 1) and (2, 2) and two of the marginal levels (1;1) and (2;2) are displayed. As shown in Figure 1, the standard deviations at the three levels under the general multi-arm covariate-adaptive randomization and stratified permuted block randomization remain unchanged nearly, depicting the stability of the corresponding imbalances for both randomization procedures. As for Pocock and Simon’s procedure, the overall and marginal imbalances stabilize, whereas the standard deviations of the within-stratum imbalances increase considerably as the sample size increases, implying a convergence rate $O_P(\sqrt{n})$. These findings are consistent with those in Theorems 3.2 and 3.3.

On the other hand, although the imbalances at the three levels under the general multi-arm covariate-adaptive randomization and stratified permuted block randomization are bounded in probability, the imbalances are stabler under the general multi-arm covariate-adaptive randomization. Taking the overall imbalance for example, we see that the standard deviations with different sample sizes approximate 1 under stratified permuted block randomization, and the standard deviations are much smaller under the general multi-arm covariate-adaptive randomization, approximating 0.65.

Therefore, Pocock and Simon’s procedure misbehaves at the within-stratum level, while all of the imbalances under the general multi-arm covariate-adaptive randomization and stratified permuted block randomization are bounded in probability. However, the general multi-arm covariate-adaptive randomization outperforms the stratified permuted block randomization.

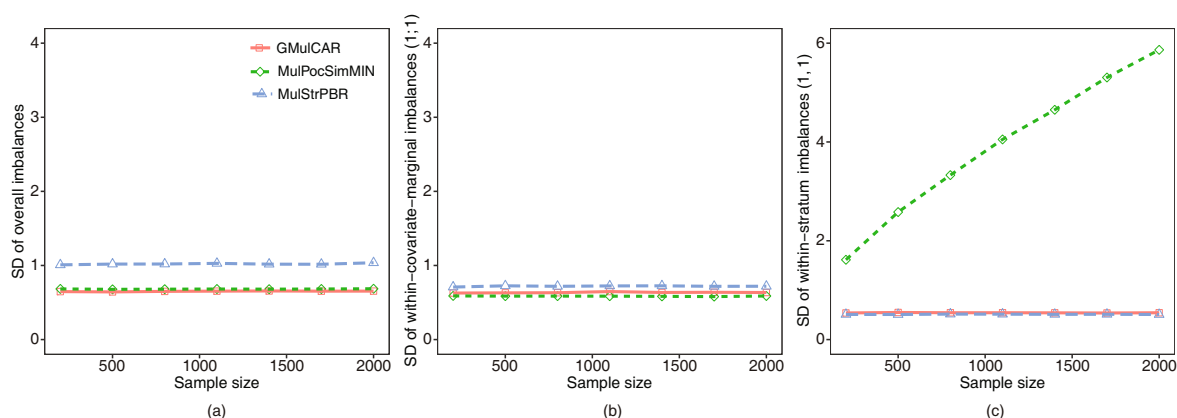


Figure 1 (Color online) The standard deviations (SDs) of $D_n^{(1)}(\cdot)$ in the case of 2×2 strata with different sample sizes under the general multi-arm covariate-adaptive randomization (GMulCAR) (a), the multi-arm Pocock and Simon’s minimization (MulPocSimMIN) procedure (b) and the multi-arm stratified permuted block randomization (MulStrPBR) (c)

4.2 The case of 2^{10} strata

We further simulate a case wherein 10 covariates with 2 levels for each covariate resulting in 1,024 strata were considered, and 600 patients were involved. The specified parameters are as follows:

- the allocation probabilities and the block size are congruent with those in Subsection 4.1;
- the weights: $w_o = 0.1$, $w_{m,i} = 0.8/10$ and $w_s = 0.1$, $i = 1, \dots, 10$ for the general multi-arm covariate-adaptive randomization; $w_o = 0$, $w_{m,i} = 1/10$ and $w_s = 0$, $i = 1, \dots, 10$ for Pocock and Simon’s procedure;
- the covariates generating process: independence assumptions between patients and between covariates within each patient are followed. Different levels within each covariate are generated with a uniform probability. Therefore, the covariate profile of the j -th patient $Z_j = (k_1, \dots, k_I)$, $j = 1, \dots, 600$, $I = 10$, is sampled from $\{1, 2\}^{10}$ independently with probability $1/1024$.

Figure 2 illustrates the mean absolute imbalances under various randomization procedures. For the same sake, we only depict the results for the treatment 1. By the Monte Carlo method, the mean absolute imbalances at corresponding levels are calculated as follows: for the overall level, we take the average of the absolute imbalances over the 10^4 simulations; for the marginal level, the mean absolute imbalance is averaged over 20 margins and over the 10^4 simulations; for the within-stratum level with $6a + i$ patients, where a is a non-negative integer and $i = 0, 1, \dots, 5$, the mean absolute imbalances are obtained by taking the average of the absolute imbalances over all the strata with $6a + i (\neq 0)$ patients and over the 10^4 simulations.

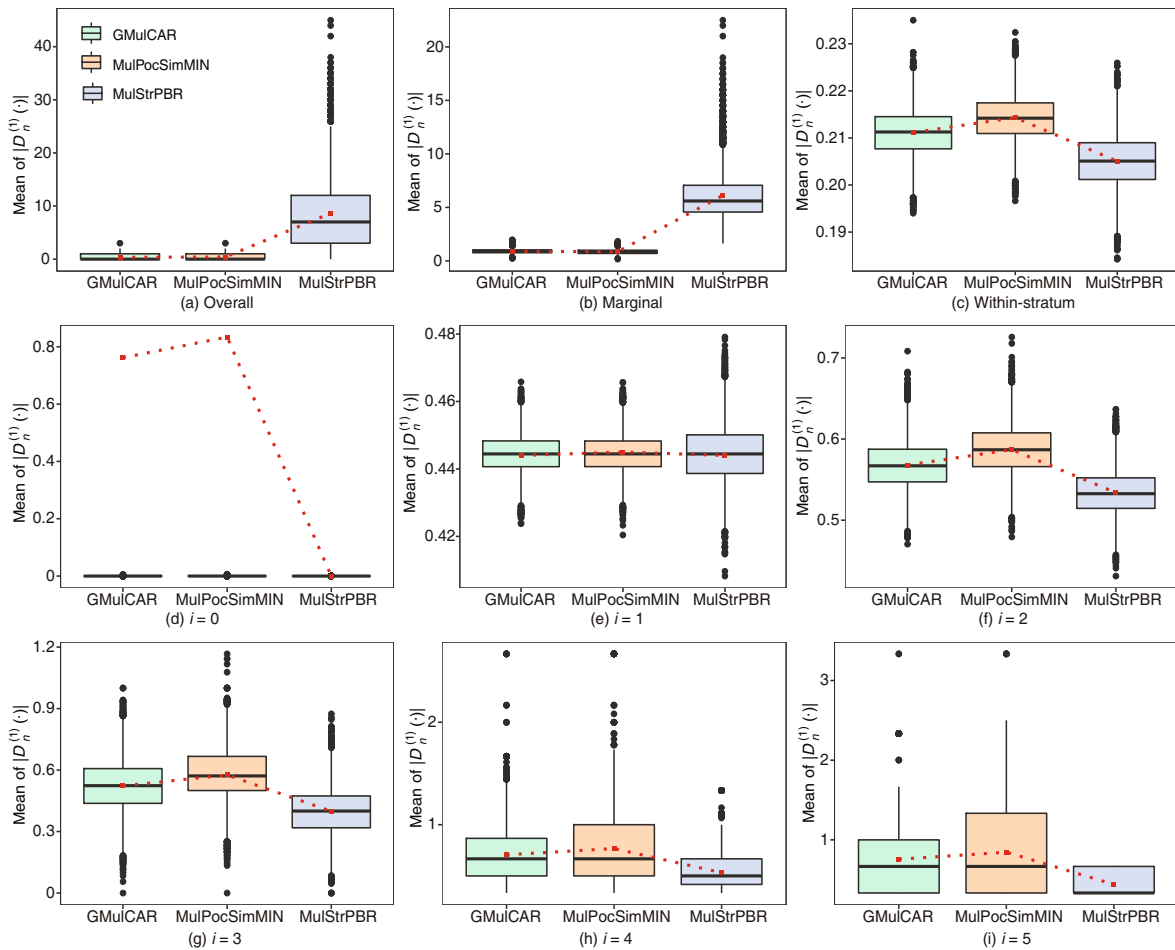


Figure 2 (Color online) The mean absolute imbalances $|D_n^{(1)}(\cdot)|$ for the treatment 1 in the case of 2^{10} strata with 600 patients under the GMulCAR, MulPocSimMIN and MulStrPBR

The subfigures in the first row of Figure 2 show the mean absolute imbalances at the overall, marginal, and within-stratum levels, respectively. As can be seen, the mean absolute imbalances at the overall and marginal levels are considerable under stratified permuted block randomization. Thus, if the number of strata is relatively large compared with the sample size, the stratified permuted block randomization fails to achieve good balances at the overall and marginal levels. Pocock and Simon's procedure consistently outperforms the general multi-arm covariate-adaptive randomization and stratified permuted block randomization at the marginal level. The general multi-arm covariate-adaptive randomization gives an overall balance advantage over the other two randomization procedures; furthermore, it is suboptimal compared with Pocock and Simon's procedure regarding balancing performances at the marginal level.

The mean absolute within-stratum imbalances among strata with $6a + i$ ($\neq 0, i = 0, 1, \dots, 5$) patients are represented, respectively, in the subfigures in the last two rows of Figure 2. The stratified permuted block randomization gives the smallest imbalances, especially at the strata with $6a$ patients. It, in fact, achieves the exact balance at the strata with $6a$ patients. The other two randomization procedures have relatively large mean absolute imbalances, and the general multi-arm covariate-adaptive randomization behaves slightly better than Pocock and Simon's procedure. However, of the 1024 strata, approximately 55.64% contains no patients, 11.7% contains more than 2 patients, and only 3.07×10^{-5} have 6 patients. Hence, the imbalances are chiefly caused by the overall and marginal levels, implying the limitation of the stratified permuted block randomization in this case.

To conclude, the general multi-arm covariate-adaptive randomization takes a significant advantage at the overall level, and no single type of imbalances becomes too extreme. Hence, the general multi-arm covariate-adaptive randomization behaves best in achieving a general balance of a trial. Pocock and Simon's procedure is preferred when clinical trialists focus on achieving marginal balances. The stratified permuted block randomization has the best performance at the within-stratum level, but it fails when the number of strata becomes considerable.

We further conduct simulation studies to explore the sensitivity of the general multi-arm covariate-adaptive randomization to different choices of weights. In general, the choice of the weights is quite flexible, and we could choose any weights according to pre-specified design objectives as long as the weights could be summed up to 1. As a matter of fact, a specific choice of weights corresponds to a specific randomization scheme, as discussed in Remark 2.1. The parameters are specified as follows:

- the allocation probabilities are congruent with those above;
 - the sample size: the sample size $n = 600$;
 - the weights: five choices of the weights are considered in the case of 2×2 strata:
 - equal weights are imposed on the within-stratum imbalance and each marginal imbalance: $(w_o, w_s, w_{m,1}, w_{m,2}) = (0.1, 0.3, 0.3, 0.3)$;
 - equal weights are imposed on each marginal imbalance and no weight is imposed on the within-stratum imbalance: $(w_o, w_s, w_{m,1}, w_{m,2}) = (0.2, 0.0, 0.4, 0.4)$;
 - solely consider the within-stratum imbalance: $(w_o, w_s, w_{m,1}, w_{m,2}) = (0.0, 1.0, 0.0, 0.0)$;
 - more weights are imposed on the within-stratum and marginal imbalances of the first covariate: $(w_o, w_s, w_{m,1}, w_{m,2}) = (0.1, 0.3, 0.5, 0.1)$;
 - more weights are imposed on the within-stratum and marginal imbalances of the second covariate: $(w_o, w_s, w_{m,1}, w_{m,2}) = (0.1, 0.3, 0.1, 0.5)$;
- also, five choices of the weights are considered in the case of 2^{10} strata:
- equal weights are imposed on the within-stratum imbalance and each marginal imbalance: $w_s = 0.3$, and $w_o = w_{m,i} = \frac{0.7}{11}, i = 1, \dots, 10$;
 - equal weights are imposed on each marginal imbalance and no weight is imposed on the within-stratum imbalance: $w_s = 0.0$, and $w_o = w_{m,i} = \frac{1.0}{11}, i = 1, \dots, 10$;
 - solely consider the within-stratum imbalance: $w_s = 1.0$, and $w_o = w_{m,i} = 0.0, i = 1, \dots, 10$;
 - more weights are imposed on the within-stratum and marginal imbalances of the first covariate: $w_s = 0.3, w_{m,1} = 0.5$, and $w_o = w_{m,i} = \frac{0.5}{11}, i = 2, \dots, 10$;
 - more weights are imposed on the within-stratum and marginal imbalances of the second covariate: $w_s = 0.3, w_{m,2} = 0.5$, and $w_o = w_{m,i} = \frac{0.5}{11}, i = 1, 3, \dots, 10$.

Table 1 The mean absolute imbalances $|D_n^{(1)}(\cdot)|$ for the treatment 1 in both cases of 2×2 and 2^{10} strata with different weights and 600 patients under the general multi-arm covariate-adaptive randomization

2×2 strata						2^{10} strata					
Weights	Mean absolute imbalances					Weights	Mean absolute imbalances				
	Overall	(1, 1)	(2, 2)	(1; 1)	(2; 2)		Overall	Level1	Level2	(1; 1)	(2; 2)
(0.1, 0.3, 0.3, 0.3)	0.40	0.45	0.44	0.46	0.46	$(\frac{0.7}{11}, 0.3, \frac{0.7}{11}, \frac{0.7}{11}, \dots)$	0.38	0.21	0.21	0.91	0.92
(0.2, 0.0, 0.4, 0.4)	0.32	2.33	2.31	0.47	0.47	$(\frac{1.0}{11}, 0.0, \frac{1.0}{11}, \frac{1.0}{11}, \dots)$	0.36	0.21	0.21	0.90	0.88
(0.0, 1.0, 0.0, 0.0)	0.76	0.40	0.40	0.57	0.57	(0.0, 1.0, 0.0, 0.0, ...)	174.54	0.24	0.23	87.26	87.22
(0.1, 0.3, 0.5, 0.1)	0.41	0.45	0.45	0.42	0.56	$(\frac{0.5}{10}, 0.3, 0.2, \frac{0.5}{10}, \dots)$	0.38	0.20	0.20	0.56	1.03
(0.1, 0.3, 0.1, 0.5)	0.41	0.46	0.45	0.56	0.41	$(\frac{0.5}{10}, 0.3, \frac{0.5}{10}, 0.2, \dots)$	0.39	0.21	0.21	1.03	0.56

Note. (1) The “Level1” corresponds to the level of (1, 1, 1, 1, 1, 1, 1, 1), and the “Level2” corresponds to the level of (2, 2, 2, 2, 2, 2, 2, 2). (2) “...” in the weights represents the weights imposed on the marginal imbalances of the last 8 covariates, the values of which are equal to the value of the weight imposed on the overall imbalance; for example, $(\frac{0.7}{11}, 0.3, \frac{0.7}{11}, \frac{0.7}{11}, \dots)$ is detailed as $(\frac{0.7}{11}, 0.3, \frac{0.7}{11}, \frac{0.7}{11}, \frac{0.7}{11}, \frac{0.7}{11}, \frac{0.7}{11}, \frac{0.7}{11}, \frac{0.7}{11}, \frac{0.7}{11}, \frac{0.7}{11}, \frac{0.7}{11})$.

For the same sake, we merely outline the mean absolute imbalances $|D_n^{(1)}(\cdot)|$ for the treatment 1 at the overall level, within two of the margins (1; 1) and (2; 2) and two of the strata ((1, 1) and (2, 2) in the case of 2×2 strata, and (1, ..., 1) and (2, ..., 2) in the case of 2^{10} strata) in Table 1. We first discuss the results in the case of 2×2 strata, in which the number of strata is moderate. As can be seen from the mean absolute overall imbalances, in the event that more weights are shifted towards the overall imbalance, we achieve a smaller one. If no weight is imposed on the within-stratum imbalance ($w_s = 0$ in the second row), the randomization method brings considerable imbalances at the within-stratum level; for comparison, if we solely consider the within-stratum imbalance ($w_s = 1$ in the third row), we achieve relatively small imbalances at all the three levels and the smallest within-stratum imbalance compared with those in the other cases. As regards the marginal level, more weights are shifted to a specific covariate ($w_{m,1} = 0.3$ in the fourth row and $w_{m,2} = 0.3$ in the fifth row), and the randomization scheme is well balanced with respect to the covariate. The general guidance concluded from these results is that if a covariate is predetermined to be important, more weights can be imposed on the within-stratum and marginal imbalances of the covariate.

As for the case of 2^{10} strata, the similar conclusions can be drawn for the overall and marginal levels. It is worth noting that, however, if we only consider the within-stratum imbalances ($w_s = 1$ in the third row), almost negligible reduction in the within-stratum imbalances is achieved at the cost of considerable increases in the overall and marginal imbalances. This is because when the number of strata is relatively large compared with the sample size, most strata contain no patients or very few patients, such as 1 patient; then the reduction in the within-stratum imbalances is extremely limited. These results agree with our discussion about the choice of weights in Remark 3.7.

4.3 An example mimicking real clinical data

In this subsection, we illustrate the advantages of the general multi-arm covariate-adaptive randomization procedure by mimicking a clinical study of the brief intervention [7]. The study was conducted to contrast the effects of a brief intervention with telephone boosters (BI-B), with those of screening, assessment and referral (SAR) to treatment and minimal screening only (MSO) among drug using. In total, 1,285 patients have been chosen for the study. For each patient, 9 categorical covariates are considered, such as the sex, race and marital status. For ease of reading, we only select 8 covariates of interest and approximate the distribution in Table 2 based on the original study. Since some levels of some margins are with a low account, resulting in considerably low probability to the corresponding stratum, we combine these levels as a category. For example, we view the levels of American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Other, Multiracial and Unknown within the margin of race, as a category of Others.

Table 2 Baseline characteristics and the distribution for the clinical trial of the brief intervention

Characteristic		Proportion
Sex	Male	70%
	Female	30%
Ethnicity	Hispanic or Latino	24%
	Not Hispanic or Latino	76%
Race	Black or African American	34%
	White	50%
	Others	16%
Education completed	1–11 y	32%
	General Educational Development (GED)/12 y	32%
	Some college or above	36%
Marital status	Married	19%
	Widowed, separated, or divorced	21%
	Never married	60%
Employment in the past 3 y	Full-time, homemaker, or student	38%
	Part-time or retired/disable	37%
	Unemployed or in controlled environment	25%
Annual household income	\$0–\$15,000	62%
	> \$15,000	26%
	Declined to answer	12%
Primary substance	Cannabis	44%
	Cocaine	27%
	Others	29%

Table 3 The distribution of patients among 2,916 strata for the clinical trial of the brief intervention

# of patients within-stratum	0	1	2	3	4	5	6
Proportion	73.0%	17.8%	5.3%	2.0%	0.9%	0.4%	0.2%
# of strata	938.1	228.7	68.1	25.7	11.6	5.1	2.6

Note. # of patients within-stratum: the number of patients within-stratum; # of strata: the number of strata.

For simplicity, we assume independence between covariates. Thus, the distribution of each stratum can be calculated easily with the product of corresponding marginal distributions. Then the covariate profile of each patient is simulated from a multinomial distribution generated according to Table 2. In this simulation study, the allocation probabilities and the block size are congruent with those in Subsection 4.1.

Table 3 presents the distribution of 1,285 patients among 2,916 strata. In this simulated case, 73% of the strata contain no patients, 17.8% contain 1 patient, 8.6% contain 2, 3, 4 or 5 patients, and 0.6% have 6 or more patients, in which only 0.2% of the strata contain exactly 6 patients. For stratified permuted block randomization, it is of high risk to cause imbalances within the strata with 2, 3, 4 or 5 patients. Although this method behaves entirely well in a complete block, the effect is almost negligible in this case. The incomplete blocks further result in a massive imbalance at the overall level. Moreover, few weights should be imposed on the within-stratum imbalances, as discussed in Remark 3.7. In the event that the primary substance is determined of significant importance, more weights should be shifted towards the marginal imbalance of this covariate. Then we set $w_{m,8} = 0.3$, $w_s = 0.1$ and $w_o = w_{m,i} = 0.6/8$, $i = 1, \dots, 7$ for the general multi-arm covariate-adaptive randomization procedure. For comparison, we also explored the performance of Pocock and Simon’s procedure with $w_{m,8} = 0.3$ as well as $w_{m,i} = 0.7/7$, $i = 1, \dots, 7$.

The variances of numbers of patients in each treatment at the three levels are compared (i.e., the overall number $N_n^{(t)}$, the marginal number $N_n^{(t)}(i, k_i)$ and the within-stratum number $N_n^{(t)}(k_1, \dots, k_I)$, $t = 1, 2, 3$) and are outlined in Tables 4–6, respectively. Table 4 illustrates the mean, median and

Table 4 Comparison for variances of the overall numbers of patients in the three treatments: $N_{1285}^{(t)}$ ($t = 1, 2, 3$) among various randomization methods

	GMulCAR	MulPocSimMIN	MulStrPBR
Mean	0.79	0.88	311.96
Median	0.33	0.33	214.33
95%-quantile	2.33	2.33	937.33

Table 5 Comparison for variances of the marginal numbers of patients in the three treatments: $N_{1285}^{(t)}(i; k_i)$ ($t = 1, 2, 3$) among various randomization methods

Characteristic		GMulCAR	MulPocSimMIN	MulStrPBR
Sex	Male	2.10	1.80	203.83
	Female	2.09	1.81	107.92
	Average mean variance	2.10	1.80	155.88
Ethnicity	Hispanic or Latino	2.13	1.78	89.23
	Not Hispanic or Latino	2.16	1.78	222.19
	Average mean variance	2.14	1.78	155.71
Race	Black or African American	2.67	2.21	112.75
	White	2.66	2.24	144.00
	Others	2.66	2.21	58.61
	Average mean variance	2.66	2.22	105.12
Employment in the past 3 y	Full-time, homemaker, or student	2.65	2.20	101.97
	Part-time, or retired/disable	2.66	2.24	102.59
	Unemployed or in controlled environment	2.65	2.25	108.09
	Average mean variance	2.65	2.23	104.22
Education completed	1-11 y	2.64	2.23	70.50
	General Educational Development (GED)/12 y	2.63	2.20	76.78
	Some college or above	2.65	2.26	165.45
	Average mean variance	2.64	2.23	104.24
Marital status	Married	2.69	2.22	113.67
	Widowed, separated, or divorced	2.67	2.18	113.41
	Never married	2.65	2.23	84.74
	Average mean variance	2.67	2.21	103.94
Annual household income	\$0 – \$15,000	2.64	2.20	174.50
	> \$15,000	2.61	2.20	92.41
	Declined to answer	2.63	2.23	47.49
	Average mean variance	2.63	2.21	104.80
Primary substance	Cannabis	0.74	0.80	127.03
	Cocaine	0.74	0.80	90.06
	Others	0.74	0.80	94.83
	Average mean variance	0.74	0.80	103.97

95%-quantile of the variances of overall numbers of patients in the three treatments. The general multi-arm covariate-adaptive randomization procedure achieves the smallest mean, median and 95%-quantile of the variances, while those under Pocock and Simon's procedure are slightly larger. Moreover, the mean overall variances under both procedures are smaller than those in the clinical study, wherein 427, 427 and 431 patients are allocated to the three different treatments, respectively, and thus result in the overall variance ($32/6 = 16/3$). As can be seen, all of the three quantities are extremely large for the stratified permuted block randomization.

Table 6 Comparison for variances of the within-stratum numbers of patients in the three treatments: $N_{1285}^{(t)}(k_1, \dots, k_I)$ ($t = 1, 2, 3$) among various randomization methods

# of patients	GMulCAR	MulPocSimMIN	MulStrPBR
$6a + 0$	0.00	0.01	0.00
$6a + 1$	0.34	0.35	0.33
$6a + 2$	0.59	0.69	0.53
$6a + 3$	0.77	1.02	0.60
$6a + 4$	0.92	1.34	0.54
$6a + 5$	1.04	1.64	0.33

Note. a is a non-negative integer.

Table 5 summarizes the mean marginal variances, which are calculated by taking an average over 10^4 simulations of the variance of the numbers of patients in the three treatments within a specific covariate at different levels. We also outline the average mean variance by taking the average of mean variances over all the levels within a particular covariate. It can be seen that the mean variance at all the levels of each covariate is the smallest under Pocock and Simon's procedure, and thus the smallest average mean variance, whereas the mean variances under the general procedure are slightly larger, resulting in a slightly larger average mean variance. However, considerable mean variances and thus average mean variances are obtained under stratified permuted block randomization. Therefore, Pocock and Simon's procedure has a balance advantage over the general procedure and stratified permuted block randomization at the marginal level; the general multi-arm covariate-adaptive randomization performs acceptably worse; the stratified permuted block randomization fails to achieve the marginal balance in this case. On the other hand, the covariate imbalances of primary substance reduce more significantly due to the more weights imposed on this covariate. The result agrees with the discussion in Remark 3.7.

We average the variances of the numbers of patients in the three treatments over 10^4 simulations and over the strata with $6a + i$ patients, where a is a non-negative integer and $i = 0, 1, 2, \dots, 5$, which are shown in Table 6. Among the strata containing 3, 4, 5 and 6 patients, the stratified permuted block randomization procedure achieves the minimum mean variance, especially 0 for strata with exactly $6a$ patients, whereas under the general procedure, slightly larger values of the mean variances are achieved. As for the variances among strata including 2 patients for the general procedure and the stratified permuted block randomization, the 2 involved patients assigned to different treatments would make the smallest imbalances at overall, marginal and within-stratum levels; thus the minimum imbalance is achieved on the whole defined in Step (5). Therefore, the stratified permuted block randomization causes relatively larger variances because of the randomness of choosing blocks. Under Pocock and Simon's procedure, all the mean variances are a bit larger among the three randomized procedures. Thus it is not effective in achieving the within-stratum balance.

To conclude, although the stratified permuted block randomization performs outstandingly at the within-stratum level, it is not recommended in this case. There are two reasons: firstly, the stratified permuted block randomization behaves somewhat worse at both overall and marginal levels with fairly significant variances; secondly, an extremely small percentage of strata contain over 6 patients. Thus, the advantage at the within-stratum level can be ignored. Pocock and Simon's procedure is more applicable to this case than the stratified permuted block randomization, but it has relatively large variances at the within-stratum level. In contrast to the stratified permuted block randomization and Pocock and Simon's procedure, the balancing performances at the three levels are satisfactory under the general multi-arm covariate-adaptive randomization procedure. Therefore, the general multi-arm covariate-adaptive randomization procedure takes a general balance advantage.

5 Concluding remarks

In this paper, we study the theoretical properties of a general family of multi-arm covariate-adaptive designs. These results provide a unified and fundamental theory about the balance properties of covariate-

adaptive randomization procedures. In the literature, it is well known that the imbalance is a positive recurrent Markov chain for Efron's biased coin design (without involving covariates) [12]. Markaryan and Rosenberger [24] studied some exact properties of Efron's biased coin design. Hu and Hu [19] showed that the imbalances $(\mathbf{D}_n)_{n \geq 1}$ are positive recurrent Markov chains for a very limited family of two-arm covariate-adaptive designs with Efron's biased coin allocation function. The condition (C) in their paper is too restrictive, and it is almost impossible to check this condition in real applications. The proposed general multi-arm randomization procedure in this paper includes the two-arm case proposed by Hu and Hu [19], and the results in this paper also provide new insights into imbalances under covariate-adaptive randomization procedures: (i) when $w_s > 0$ (the within-stratum weight is positive), the imbalances $(\mathbf{D}_n)_{n \geq 1}$ are positive recurrent Markov chains, and therefore, all the three types of imbalances (within-stratum, marginal and overall) are bounded in probability; (ii) when $w_s = 0$ and $w_{m,i} > 0$, then the marginal (the i -th covariate) and overall imbalances are bounded in probability, but the within-stratum imbalance is not; (iii) when $w_s = w_{m,i} = 0$ for all $i = 1, \dots, I$ and $w_0 = 1$, only the overall imbalance is bounded in probability.

It is very important to understand statistical inferences under covariate-adaptive randomization. Birkett [6] and Forsythe [14] have raised concerns about the conservativeness of the unadjusted analysis (such as two-sample t-test) under covariate-adaptive randomization based on simulation studies. Shao et al. [35] studied this problem theoretically under a very special covariate-adaptive biased coin randomization procedure, which is a stratified randomization procedure and only applies to a single covariate case. Also, they focused on a simple homogeneous linear model and only considered a two-sample t-test. Ma et al. [22] derived the asymptotic distributions of the test statistics of testing both the treatment effects and the significance of covariates under null and alternative hypotheses for a large family of two-arm covariate-adaptive randomization procedures, while Zhu and Hu [47] focused on the sequential statistics instead of on the final test statistic and derived the joint distribution of the sequential test statistics for several scenarios. However, the theoretical properties induced in [22, 47] are based on the assumptions that the overall and marginal imbalances are bounded in probability, which were only verified for Pocock and Simon's procedure with two treatments in [22]. In this paper, we derive the comprehensive theoretical properties under a broad spectrum of covariate-adaptive randomization, including the two-arm case, and thus providing a theoretical foundation for existing statistical inferences. Ma et al. [23] loosed the strong balancing assumptions and derived the properties of statistical inferences following general covariate-adaptive randomization (CAR) procedures under the linear model framework. However, most of the discussion about statistical inferences for covariate-adaptive randomized clinical trials in the literature is limited to the two-arm case. The theoretical properties for statistical inferences under multi-arm covariate-adaptive randomization are rarely touched. Based on the work of [8], Bugni et al. [9] generalized the results to the multi-arm case. However, the discussion focused on a single special case of covariate-adaptive randomization. This is because the theoretical properties of multi-arm covariate-adaptive randomization procedures are usually not available in the literature. The results in this paper open the door to study the theoretical behavior of classical statistical inferences under multi-arm covariate-adaptive randomization. For example, based on Corollary 3.8, we can study the behavior of testing hypotheses and other methods under Pocock and Simon's procedure with multiple treatments. We leave these as future research projects.

In this paper, we only consider balancing discrete (categorical) covariates. In the literature, continuous covariates are typically discretized in order to be included in the randomization scheme [37]. We may apply the proposed designs to balancing continuous covariates after discretization. However, as discussed in [33], the breakdown of a continuous covariate into subcategories means increased effort and loss of information. Ciolino et al. [10] also pointed out the lack of publicity for practical methods for continuous covariate balancing and lack of knowledge on the cost of failing to balance continuous covariates. We may consider balancing continuous covariates under a similar framework to that in this paper. However, it is usually challenging to obtain the corresponding theoretical properties. There are not many studies in the literature.

The proposed procedures and their properties may be generalized in several ways. First, we may

apply the same idea to problems of unequal ratios [16]. Sometimes, if one treatment is superior to (or less costly than) the other, then assigning more patients to the treatment would be more ethical (economical). Second, we may combine the idea in this paper with the efficient randomized-adaptive designs (ERADE) of [18] to obtain a new family of covariate-adjusted response-adaptive (CARA) randomization procedures [45]; it could be a real challenge to study the corresponding theoretical properties. Third, we only consider the fixed weights in this paper. It is, however, of great importance and interest to determine the values of the weights based on specific data to better achieve pre-specified randomization objects, such as the good balance of a specific covariate. Therefore, we may propose a data-driven covariate-adaptive randomization design in which the weights are sequentially modified based on the accrued data information and explore theoretical properties. Finally, we derive the asymptotic normality for the within-stratum imbalances. However, the close formula of the asymptotic variances remains unknown, which is the grounding of statistical inferences. Little research about the statistical inferences for multi-arm covariate-adaptive randomization is available heretofore. It thus would be an interesting topic to extend our work to obtain the close formula of the asymptotic variances for within-stratum imbalances and further establish the theoretical properties for statistical inferences under our proposed general multi-arm covariate-adaptive randomization procedure in the future. We leave all these as future research topics.

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Appendix A Proofs

Our proofs are based on the properties of Markov chains on a finite state space. For simplification, we write $\mathbf{k} = (k_1, \dots, k_I)$. Let $\Delta\mathcal{D}$ be the state space of $\Delta\mathbf{D}_n = \mathbf{D}_n - \mathbf{D}_{n-1}$, i.e., each $\mathbf{d} \in \Delta\mathcal{D}$ is in the form

$$d_n^{(t)}(\mathbf{k}) = \begin{cases} 1 - \frac{1}{T} & \text{for a specific } \mathbf{k} \text{ and a specific } t, \\ -\frac{1}{T} & \text{for a specific } \mathbf{k}, \\ 0 & \text{for others.} \end{cases}$$

Proof of Proposition 3.1. For (i), based on the fact that

$$\begin{aligned} D_n^{(t)} &= \sum_{\mathbf{k}} D_n^{(t)}(\mathbf{k}), \\ D_n^{(t)} &= \sum_{k_i=1}^{m_i} D_n^{(t)}(i; k_i), \quad \forall i = 1, \dots, I, \\ D_n^{(t)}(i; k_i) &= \sum_{\mathbf{k} \setminus k_i} D_n^{(t)}(\mathbf{k}), \quad \forall k_i, i = 1, \dots, T, \end{aligned}$$

where $\sum_{\mathbf{k} \setminus k_i}$ means that taking summation over all $k_1, \dots, k_{i-1}, k_{i+1}, \dots, k_I$, and then taking the summation of $\Lambda_n^{(t)}(\mathbf{k})$ over all \mathbf{k} yields

$$\sum_{\mathbf{k}} \Lambda_n^{(t)}(\mathbf{k}) = \left(w_o m + \sum_{i=1}^I w_{m,i} \prod_{j \neq i} m_j + w_s \right) D_n^{(t)}, \quad \forall t = 1, \dots, T. \tag{A.1}$$

Let $i(\mathbf{k}, t)$ be the index of $D_n^{(t)}(\mathbf{k})$ in \mathbf{D}_n . Define $\mathbf{x} \in \mathbb{R}^{T \times m}$, of which the $i(\mathbf{k}, t)$ -th ($\forall \mathbf{k}$) elements are 1 and others are 0. For two vectors $\mathbf{a} = (a_l, l = 1, \dots, T \times m)$ and $\mathbf{b} = (b_l, l = 1, \dots, T \times m)$ on $\mathbb{R}^{T \times m}$, we write

$$\mathbf{a} \cdot \mathbf{b} = \sum_{\mathbf{k}} a_{i(\mathbf{k}, t)} b_{i(\mathbf{k}, t)}$$

for any fixed t ($t = 1, \dots, T$). Thus (A.1) can be written as

$$\mathbf{x} \cdot \Lambda_n = \left(w_o m + \sum_{i=1}^I w_{m,i} \prod_{j \neq i} m_j + w_s \right) D_n^{(t)}, \quad \forall t = 1, \dots, T.$$

So $D_n^{(t)}$ is a linear transformation of Λ_n . Taking the summation of $\Lambda_n^{(t)}(\mathbf{k})$ over all k_1, \dots, k_I except k_i yields

$$\sum_{\mathbf{k} \setminus k_i} \Lambda_n^{(t)}(\mathbf{k}) = \left(w_o \prod_{j \neq i} m_j + \sum_{l \neq i} w_{m,l} \prod_{j \neq i, l} m_j \right) D_n^{(t)} + \left(w_{m,i} \prod_{j \neq i} m_j + w_s \right) D_n^{(t)}(i; k_i), \tag{A.2}$$

which is true for all k_i and $i = 1, \dots, I, t = 1, \dots, T$. Similarly, define $\mathbf{y} \in \mathbb{R}^{T \times m}$, of which the $i(\mathbf{k}, t)$ -th ($\forall \mathbf{k}$ with the fixed k_i) elements are 1 and others are 0. Then (A.2) can be written as

$$\mathbf{y} \cdot \Lambda_n = \left(w_o \prod_{j \neq i} m_j + \sum_{l \neq i} w_{m,l} \prod_{j \neq i, l} m_j \right) D_n^{(t)} + \left(w_{m,i} \prod_{j \neq i} m_j + w_s \right) D_n^{(t)}(i; k_i).$$

Thus, when $w_{m,i} + w_s > 0$, each $D_n^{(t)}(i; k_i)$ is a linear transformation of Λ_n and $D_n^{(t)}$, so it is a linear transformation of Λ_n . Finally, when $w_s > 0$, it is obvious from the definition of $\Lambda_n^{(t)}(\mathbf{k})$ that for all \mathbf{k} and $t = 1, \dots, T$, each $D_n^{(t)}(\mathbf{k})$ is a linear transformation of $\Lambda_n^{(t)}(\mathbf{k})$, $D_n^{(t)}(1; k_1), \dots, D_n^{(t)}(I; k_I)$ and $D_n^{(t)}$, and hence it is a linear transformation of Λ_n . Therefore, when $w_s > 0$, $\Lambda_n = \mathbf{L}(\mathbf{D}_n)$ is a one-to-one linear map.

For (ii) and (iii), it is sufficient to show the Markov property. Note that

$$D_n^{(t)}(\mathbf{k}) = D_{n-1}^{(t)}(\mathbf{k}) + \left(\mathbb{I}_{(T_n=t)} - \frac{1}{T} \right) \mathbb{I}_{(Z_n=\mathbf{k})}.$$

We know that the allocation probability $p_{n,t}$ is a function of Λ_{n-1} . For any fixed \mathbf{k} , let $\mathbf{d}_{\mathbf{k}} \in \mathbb{R}^{T \times m}$, of which the $i(\mathbf{k}, t)$ -th ($\forall t = 1, \dots, T$) elements are 1 and others are 0. Also, for two arbitrary vectors \mathbf{x} and \mathbf{y} , we define an operator \circ such that

$$\mathbf{x} \circ \mathbf{y} = \{x_i y_i : x_i y_i \neq 0\}.$$

Then we further define the function $r_{n-1,t}(\mathbf{k})$ that returns to the ranking of $\Lambda_{n-1}^{(t)}(\mathbf{k})$ in the increasing order among

$$\mathbf{d}_{\mathbf{k}} \circ \Lambda_{n-1} = \{\Lambda_{n-1}^{(t')} : 1 \leq t' \leq T\},$$

which can be written as $r(\Lambda_{n-1}^{(t)}(\mathbf{k}), \mathbf{d}_{\mathbf{k}} \circ \Lambda_{n-1})$, i.e., $r_{n-1,t'}(\mathbf{k}) = s$ if $\Lambda_{n-1}^{(t')}(\mathbf{k}) = \Lambda_{n-1}^{((s))}(\mathbf{k})$, $s, t' = 1, \dots, T$. Hence,

$$P\left(\Delta D_n^{(t)}(\mathbf{k}) = 1 - \frac{1}{T} \mid \mathcal{F}_{n-1}\right) = P(T_n = t, Z_n = \mathbf{k} \mid \mathcal{F}_{n-1}) = p_{r_{n-1,t}(\mathbf{k})} p(\mathbf{k}), \tag{A.3}$$

$$P\left(\Delta D_n^{(t)}(\mathbf{k}) = -\frac{1}{T} \mid \mathcal{F}_{n-1}\right) = P(T_n \neq t, Z_n = \mathbf{k} \mid \mathcal{F}_{n-1}) = (1 - p_{r_{n-1,t}(\mathbf{k})}) p(\mathbf{k}) \tag{A.4}$$

and

$$P(\Delta D_n(\mathbf{k}) = 0 \mid \mathcal{F}_{n-1}) = P(Z_n \neq \mathbf{k} \mid \mathcal{F}_{n-1}) = 1 - p(\mathbf{k}). \tag{A.5}$$

Define $\mathbf{d}_{1/T} \in \mathbb{R}^{T \times m}$, of which for any fixed \mathbf{k} , the $i(\mathbf{k}, t')$ -th ($\forall t' = 1, \dots, T$) elements are $1/T$ and others are 0 (only T elements are nonzero). Also, let $\mathbf{v}_1 \in \mathbb{R}^{T \times m}$, of which the $i(\mathbf{k}', t')$ -th ($\forall \mathbf{k}'$) elements are t' for all $t' = 1, \dots, T$. Let $\mathbf{v}_2 \in \mathbb{R}^{T \times m}$, of which the $i(\mathbf{k}', t')$ -th ($\forall t' = 1, \dots, T$) elements are $p(\mathbf{k}')$ for all \mathbf{k}' . Let $\mathbf{v}_3 \in \mathbb{R}^{T \times m}$, of which the $i(\mathbf{k}', t')$ -th ($\forall t' = 1, \dots, T$) elements are \mathbf{k}' for all \mathbf{k}' . Define

$$\bar{\mathbf{t}} = (\mathbf{d} + \mathbf{d}_{1/T}) \cdot \mathbf{v}_1$$

and

$$\bar{\mathbf{k}} = (\mathbf{d} + \mathbf{d}_{1/T}) \cdot \mathbf{v}_3.$$

Then we can conclude that

$$P(\Delta \mathbf{D}_n = \mathbf{d} \mid \mathcal{F}_{n-1}) = p_{r_{n-1,\bar{\mathbf{t}}}(\bar{\mathbf{k}})} |(\mathbf{d} + \mathbf{d}_{1/T}) \cdot \mathbf{v}_2| = p_{r(\Lambda_{n-1}^{(\bar{\mathbf{t}})}(\bar{\mathbf{k}}), \mathbf{d}_{\bar{\mathbf{k}}} \circ \mathbf{L}(\mathbf{D}_{n-1}))} |(\mathbf{d} + \mathbf{d}_{1/T}) \cdot \mathbf{v}_2|, \tag{A.6}$$

which depends only on $\Lambda_{n-1} = \mathbf{L}(\mathbf{D}_{n-1})$ and is positive. Thus, conditional on \mathbf{D}_{n-1} , \mathbf{D}_n is conditionally independent of $(\mathbf{D}_1, \dots, \mathbf{D}_{n-2})$. It follows that $(\mathbf{D}_n)_{n \geq 1}$ is a Markov chain on $\mathbb{R}^{T \times m}$ and is irreducible.

For the period, assume that the initial state of $(\mathbf{D}_n)_{n \geq 1}$ is \mathbf{D}_0 , whose $i(\mathbf{k}', t')$ -th element is written as $y_t^{\mathbf{k}'}$ for all \mathbf{k}' and $t' = 1, \dots, T$. For example,

$$\mathbf{D}_0 = (y_1^{\mathbf{k}_1}, \dots, y_1^{\mathbf{k}_m}, \dots, y_T^{\mathbf{k}_1}, \dots, y_T^{\mathbf{k}_m}),$$

and in the event that the first patient who falls within stratum \mathbf{k}^* was assigned to treatment t , then we got \mathbf{D}_1 , whose $i(\mathbf{k}^*, t)$ -th element is $y_t^{\mathbf{k}^*} + 1 - \frac{1}{T}$, the $i(\mathbf{k}^*, t')$ -th ($t' \neq t$) elements are $y_t^{\mathbf{k}^*} - \frac{1}{T}$, and the others are 0. For example, if $\mathbf{k}^* = \mathbf{k}_1$ and $t' = 1$, then

$$\mathbf{D}_1 = \left(y_1^{\mathbf{k}_1} - \frac{1}{T} + 1, 0, \dots, 0; y_2^{\mathbf{k}_1} - \frac{1}{T}, 0, \dots, 0; \dots; y_T^{\mathbf{k}_1} - \frac{1}{T}, 0, \dots, 0 \right).$$

Hence, starting with \mathbf{D}_1 , we can see that it takes at least $T - 1$ more steps to return to \mathbf{D}_0 , in the event where all of the next $T - 1$ patients fall within \mathbf{k}^* and the assignments T_2, \dots, T_T traverse $\{1, \dots, T\} \setminus t$.

It is easy to see that this case occurs with positive probability. In other cases, it will take s steps to return to the initial state, where s is a multiple of T . It follows that the period of $(\mathbf{D}_n)_{n \geq 1}$ is T . From (A.3)–(A.5), it is easily seen that the transition probabilities of

$$\Pi \mathbf{D} \triangleq (D_n^{\Pi(1)}(\mathbf{k}), \dots, D_n^{\Pi(T)}(\mathbf{k}) : 1 \leq k_i \leq m_i, 1 \leq i \leq I)_{n \geq 1}$$

are the same for any permutation $\Pi(1), \dots, \Pi(T)$ of $1, \dots, T$.

For (iii), we consider a more general case. Let $\tilde{\mathbf{D}} = \mathbf{F}(\mathbf{D})$ be a linear transformation of \mathbf{D} . We consider the chain $\mathbf{E}_n = (\tilde{\mathbf{D}}_n, \mathbf{\Lambda}_n)$. For any \mathbf{e} in the state space $\{(\mathbf{F}(\mathbf{d}), \mathbf{L}(\mathbf{d})) : \mathbf{d} \in \Delta \mathcal{D}\}$ of \mathbf{E}_n ,

$$P(\Delta \mathbf{E}_n = \mathbf{e} \mid \mathcal{F}_{n-1}) = \sum_{\mathbf{d} \in \Delta \mathcal{D} : (\mathbf{F}(\mathbf{d}), \mathbf{L}(\mathbf{d})) = \mathbf{e}} P(\Delta \mathbf{D}_n = \mathbf{d} \mid \mathcal{F}_{n-1}). \tag{A.7}$$

According to (A.6), we obtain that (A.7) depends on $\mathbf{\Lambda}_{n-1}$ and is positive. So, conditional on \mathbf{E}_{n-1} , \mathbf{E}_n is conditionally independent of $(\mathbf{E}_1, \dots, \mathbf{E}_{n-2})$. It follows that

$$(\mathbf{E}_n = (\mathbf{F}(\mathbf{D}_n), \mathbf{\Lambda}_n))_{n \geq 1} \text{ is an irreducible Markov chain with period } T. \tag{A.8}$$

Also, it is easily seen that for any permutation $\Pi(1), \dots, \Pi(T)$ of $1, \dots, T$, the transition probabilities of

$$\Pi \mathbf{E} \triangleq (\mathbf{F}(\Pi \mathbf{D}), \mathbf{L}(\Pi \mathbf{D}))$$

are the same. □

Proof of Theorem 3.2. Define

$$V_n = \sum_{t=1}^T \left\{ w_o [D_n^{(t)}]^2 + \sum_{i=1}^I \sum_{k_i=1}^{m_i} w_{m,i} [D_n^{(t)}(i; k_i)]^2 + w_s \sum_{\mathbf{k}} [D_n^{(t)}(\mathbf{k})]^2 \right\}.$$

We write

$$\mathbf{D} = [D^{(t)}(\mathbf{k}) : 1 \leq t \leq T, 1 \leq k_i \leq m_i, 1 \leq i \leq I],$$

and define $\mathbf{\Lambda}$ and V with \mathbf{D} taking the place of \mathbf{D}_n . By Proposition 3.1(i), V_n is a function of $\mathbf{\Lambda}_n$. We write

$$V_n = V(\mathbf{\Lambda}_n).$$

We prove the theorem via two steps. First, we show that there are a bounded set \mathcal{C} and a constant b for which

$$P_\lambda V(\mathbf{\Lambda}) - V(\mathbf{\Lambda}) \leq -1 + b \mathbb{1}_{\mathbf{\Lambda} \in \mathcal{C}}, \tag{A.9}$$

where P_λ is the transition probability matrix of $\mathbf{\Lambda}$, i.e.,

$$P_\lambda V(\mathbf{\Lambda}) = \sum_{\mathbf{\Lambda}' \in \mathcal{L}(\mathbb{R}^{T \times m})} P_\lambda(\mathbf{\Lambda}, \mathbf{\Lambda}') V(\mathbf{\Lambda}'),$$

and $P_\lambda(\mathbf{\Lambda}, \mathbf{\Lambda}')$ is the transition probability from state $\mathbf{\Lambda}$ to state $\mathbf{\Lambda}'$. In the second step, we show that for any integer $r \geq 2$, there are a bounded set \mathcal{C} and a constant b for which

$$P_\lambda V^{r+1}(\mathbf{\Lambda}) - V^{r+1}(\mathbf{\Lambda}) \leq -[V(\mathbf{\Lambda}) + 1]^r + b \mathbb{1}_{\mathbf{\Lambda} \in \mathcal{C}}. \tag{A.10}$$

The drift condition (A.9) is utilized to show the convergence in probability, and the refined drift condition (A.10) is utilized to show the convergence of moments. In fact, (A.9) implies that $(\mathbf{\Lambda}_n)_{n \geq 1}$ is a positive (Harris) recurrent Markov chain (see [26, Theorem 11.3.4]), so it is bounded in probability and has an invariant probability measure π_λ . On the other hand, by (A.10) and [26, Theorem 14.3.7] we conclude that $\pi_\lambda [V(\mathbf{\Lambda} + 1)]^r \leq b$, which implies that

$$\sup_n E(V(\mathbf{\Lambda}_n) + 1)^r < \infty \tag{A.11}$$

by [26, Theorem 14.3.6]. Notice that by Cauchy’s inequality,

$$\begin{aligned} |\Lambda_n^{(t)}(\mathbf{k})|^2 &\leq \left(w_o |D_n^{(t)}| + \sum_{i=1}^I w_{m,i} |D_n^{(t)}(i; k_i)| + w_s |D_n^{(t)}(\mathbf{k})| \right)^2 \\ &\leq \left(w_o |D_n^{(t)}|^2 + \sum_{i=1}^I w_{m,i} |D_n^{(t)}(i; k_i)|^2 + w_s |D_n^{(t)}(\mathbf{k})|^2 \right) \left(w_o + \sum_{i=1}^I w_{m,i} + w_s \right) \\ &= w_o |D_n^{(t)}|^2 + \sum_{i=1}^I w_{m,i} |D_n^{(t)}(i; k_i)|^2 + w_s |D_n^{(t)}(\mathbf{k})|^2, \end{aligned}$$

which implies that $\|\Lambda_n\|^2 \leq mV(\Lambda_n)$. It follows that $\sup_n \mathbb{E}\|\Lambda_n\|^{2r} < \infty$. Thus, we conclude that $(\Lambda_n)_{n \geq 1}$ is a positive recurrent Markov chain with $\mathbb{E}\|\Lambda_n\|^r = O(1)$ for all $r > 0$. (i)–(iii) follow from Proposition 3.1(i).

Now, we begin the proofs of (A.9) and (A.10). Given $Z_n = \mathbf{k}$, if $T_n = (t)$, then

$$V_n - V_{n-1} = 2\Lambda_{n-1}^{((t))}(\mathbf{k}) + \frac{T-1}{T} \tag{A.12}$$

by the fact that

$$\sum_{t=1}^T D_n^{(t)} = 0, \quad \sum_{t=1}^T D_n^{(t)}(i; k_i) = 0$$

and

$$\sum_{t=1}^T D_n^{(t)}(\mathbf{k}) = 0.$$

Hence,

$$\mathbb{E}[V_n - V_{n-1} \mid Z_n = \mathbf{k}, T_n = (t), \mathcal{F}_{n-1}] = 2\Lambda_{n-1}^{((t))}(\mathbf{k}) + \frac{T-1}{T}.$$

It follows that

$$\mathbb{E}[V_n \mid \mathcal{F}_{n-1}] - V_{n-1} = -2S(\Lambda_{n-1}) + \frac{T-1}{T}, \tag{A.13}$$

where

$$S(\Lambda_{n-1}) = - \sum_{\mathbf{k}} \sum_{t=1}^T \Lambda_{n-1}^{((t))}(\mathbf{k}) p_t p(\mathbf{k}).$$

Recall that D_n and Λ_n are irreducible Markov chains with period T on $\mathbb{R}^{T \times m}$ and $\mathbf{L}(\mathbb{R}^{T \times m})$, respectively. Note that $V_n = V(\Lambda_n)$ is a non-negative function of Λ_n . Equation (A.13) tells us that the drift function of the Markov chain Λ_n is

$$\mathbb{E}[V(\Lambda_n) \mid \Lambda_{n-1}] - V(\Lambda_{n-1}) = \mathbb{E}[V_n - V_{n-1} \mid \mathcal{F}_{n-1}] = -2S(\Lambda_{n-1}) + \frac{T-1}{T}$$

by the Markov property, i.e.,

$$P_\lambda V(\Lambda) - V(\Lambda) = -2S(\Lambda) + \frac{T-1}{T}.$$

Next, we need to check the drift-criteria condition (A.9). It is sufficient to show that

$$\Lambda \text{ is bounded} \Leftrightarrow S(\Lambda) \text{ is bounded.} \tag{A.14}$$

Note that

$$\sum_{t=1}^T \Lambda_{n-1}^{((t))}(\mathbf{k}) = 0$$

and

$$(p_t - p_h)[\Lambda_{n-1}^{((t))}(\mathbf{k}) - \Lambda_{n-1}^{((h))}(\mathbf{k})] \leq 0.$$

We have

$$\begin{aligned} 2T \sum_{t=1}^T p_t \cdot \Lambda_{n-1}^{((t))}(\mathbf{k}) &= 2T \sum_{t=1}^T p_t \cdot \Lambda_{n-1}^{((t))}(\mathbf{k}) - 2 \left[\sum_{t=1}^T p_t \right] \left[\sum_{t=1}^T \Lambda_{n-1}^{((t))}(\mathbf{k}) \right] \\ &= \sum_{t,h=1}^T (p_t - p_h) [\Lambda_{n-1}^{((t))}(\mathbf{k}) - \Lambda_{n-1}^{((h))}(\mathbf{k})] \\ &\leq -(p_1 - p_T) [\Lambda_{n-1}^{((T))}(\mathbf{k}) - \Lambda_{n-1}^{((1))}(\mathbf{k})] \\ &\leq -(p_1 - p_T) \frac{1}{T} \sum_{t=1}^T |\Lambda_{n-1}^{((t))}(\mathbf{k})|. \end{aligned}$$

It follows that $S(\mathbf{\Lambda}_{n-1}) \geq 0$ and

$$\frac{(p_1 - p_T) \min_{\mathbf{k}} p(\mathbf{k})}{2T^2} \sum_{\mathbf{k}} \sum_{t=1}^T |\Lambda_{n-1}^{((t))}(\mathbf{k})| \leq S(\mathbf{\Lambda}_{n-1}) \leq \sum_{\mathbf{k}} \sum_{t=1}^T |\Lambda_{n-1}^{((t))}(\mathbf{k})|.$$

Hence, (A.14) is proved. From (A.14), it follows that there are a bounded set \mathcal{C} and a constant b such that the drift condition (A.9) is satisfied.

For verifying (A.10), we shall refine the drift condition (A.9). For given $Z_n = \mathbf{k}$ and $T_n = (t)$, by (A.12) we have

$$V_n = V_{n-1} + \xi + \frac{T-1}{T},$$

where $\xi = 2\Lambda_{n-1}^{((t))}(\mathbf{k})$. It is obvious by Cauchy's inequality and Equation (A.13) that

$$|\xi| = 2|\Lambda_{n-1}^{((t))}| \leq 2\sqrt{V_{n-1}} \quad \text{and} \quad \mathbb{E}[\xi \mid \mathcal{F}_{n-1}] = -2S(\mathbf{\Lambda}_{n-1}).$$

It follows that

$$\begin{aligned} V_n^{r+1} - V_{n-1}^{r+1} &= (r+1) \left(V_{n-1} + \frac{T-1}{T} \right)^r \xi \\ &\quad + \left\{ \left(V_{n-1} + \frac{T-1}{T} \right)^{r+1} - V_{n-1}^{r+1} + \sum_{i=2}^{r+1} \binom{r+1}{i} \xi^i \left(V_{n-1} + \frac{T-1}{T} \right)^{r+1-i} \right\} \\ &\leq (r+1) \left(V_{n-1} + \frac{T-1}{T} \right)^r \xi + C_r \left(V_{n-1} + \frac{T-1}{T} \right)^r, \end{aligned}$$

where C_r is a constant which depends on r . It follows that

$$\mathbb{E}[V_n^{r+1} \mid \mathcal{F}_{n-1}] - V_{n-1}^{r+1} \leq -2(r+1) \left(V_{n-1} + \frac{T-1}{T} \right)^r S(\mathbf{\Lambda}_{n-1}) + C_r \left(V_{n-1} + \frac{T-1}{T} \right)^r,$$

i.e.,

$$P_\lambda V^{r+1}(\mathbf{\Lambda}) - V^{r+1}(\mathbf{\Lambda}) \leq \left[V(\mathbf{\Lambda}) + \frac{T-1}{T} \right]^r \{-2(r+1)S(\mathbf{\Lambda}) + C_r\},$$

which together with (A.14) implies (A.10). The proof of Theorem 3.2 is now completed. □

Proof of Theorem 3.3. We first prove that

$$\sup_n \mathbb{E} \left| \frac{D_n^{(t)}(\mathbf{k})}{\sqrt{n}} \right|^r < \infty, \quad \forall \mathbf{k}, r > 0. \tag{A.15}$$

Notice that

$$D_n^{(t)}(\mathbf{k}) = D_{n-1}^{(t)}(\mathbf{k}) + \left(\mathbb{I}_{(T_n=t)} - \frac{1}{T} \right) \cdot \mathbb{I}_{Z_n=\mathbf{k}}.$$

Thus,

$$\begin{aligned} E[D_n^{(t)}(\mathbf{k}) \mid \mathcal{F}_{n-1}] &= D_{n-1}^{(t)}(\mathbf{k}) + \left(1 - \frac{1}{T}\right)p_{r_{n-1,t}(\mathbf{k})}p(\mathbf{k}) - \frac{1}{T}(1 - p_{r_{n-1,t}(\mathbf{k})})p(\mathbf{k}) \\ &= D_{n-1}^{(t)}(\mathbf{k}) + \left[p_{r_{n-1,t}(\mathbf{k})} - \frac{1}{T}\right] \cdot p(\mathbf{k}) \\ &= D_{n-1}^{(t)}(\mathbf{k}) + \bar{g}_{n-1,\mathbf{k}}^{(t)} \cdot p(\mathbf{k}), \end{aligned} \tag{A.16}$$

where $\bar{g}_{n-1,\mathbf{k}}^{(t)} = \bar{g}(\Lambda_{n-1}^{(t)}(\mathbf{k}), \mathbf{\Lambda}_{n-1}) = p_{r_{n-1,t}(\mathbf{k})} - \frac{1}{T}$, and for simplification, we write $\bar{g}_{\mathbf{k}}^{(t)} = \bar{g}(\Lambda^{(t)}(\mathbf{k}), \mathbf{\Lambda})$. Hence,

$$D_n^{(t)}(\mathbf{k}) = \sum_{l=1}^n [D_l^{(t)}(\mathbf{k}) - E(D_l^{(t)}(\mathbf{k}) \mid \mathcal{F}_{l-1})] + \sum_{l=0}^{n-1} \bar{g}_{l,\mathbf{k}}^{(t)} \cdot p(\mathbf{k}). \tag{A.17}$$

The first term on the right-hand side of (A.17) is $O(\sqrt{n})$ in L_r , because $\{D_n^{(t)}(\mathbf{k}) - E(D_n^{(t)}(\mathbf{k}) \mid \mathcal{F}_{n-1})\}$ is a sequence of bounded martingale differences. Now we consider the second term. Notice that $\bar{g}_{\mathbf{k}}^{(t)} (\leq \frac{T-1}{T})$ is bounded by 1. By (A.9) and [26, Theorem 17.4.2], there is a constant R such that Poisson’s equation

$$\hat{g} - P_\lambda \hat{g} = \bar{g}_{\mathbf{k}}^{(t)} - \pi_\lambda \bar{g}_{\mathbf{k}}^{(t)} \tag{A.18}$$

has a solution $\hat{g} = \hat{g}_{\mathbf{k}}^{(t)} = \hat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda})$ which is a function of $\mathbf{\Lambda}$ defined on the state space of $\mathbf{\Lambda}$ with $\hat{g} \leq R(V + 1)$, where P_λ is the transition probability matrix of $\mathbf{\Lambda}$. On the other hand, it is easily seen from Proposition 3.1(iii) that the transition probabilities of the Markov chain $(\mathbf{\Lambda}_n)_{n \geq 1}$ are symmetric about treatments. It follows that the invariant probability measure π_λ of $(\mathbf{\Lambda}_n)_{n \geq 1}$ is symmetric about treatments. So

$$\pi_\lambda [p_{r_{n-1,t}(\mathbf{k})}] = \frac{1}{T} \quad \text{and} \quad \pi_\lambda \bar{g}_{\mathbf{k}}^{(t)} = 0.$$

It follows that

$$\hat{g} - P_\lambda \hat{g} = \bar{g}_{\mathbf{k}}^{(t)}. \tag{A.19}$$

Now, write $\hat{g}_n = \hat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n)$. It follows that

$$\begin{aligned} \sum_{l=0}^{n-1} \bar{g}_{l,\mathbf{k}}^{(t)} &= \sum_{l=0}^{n-1} \{\hat{g}_l - P_\lambda \hat{g}_l\} = \sum_{l=0}^{n-1} \{\hat{g}_l - E[\hat{g}_{l+1} \mid \mathcal{F}_l]\} \\ &= \sum_{l=0}^{n-1} \{\hat{g}_l - E[\hat{g}_l \mid \mathcal{F}_{l-1}]\} + E\hat{g}_0 - E[\hat{g}_n \mid \mathcal{F}_{n-1}]. \end{aligned}$$

Hence, for any $r \geq 1$,

$$\begin{aligned} E \left| \frac{1}{\sqrt{n}} \sum_{l=0}^{n-1} \bar{g}_{l,\mathbf{k}}^{(t)} \right|^{2r} &\leq C \frac{1}{n^r} E \left| \sum_{l=0}^{n-1} \{\hat{g}_l - E[\hat{g}_l \mid \mathcal{F}_{l-1}]\} \right|^{2r} + C \frac{1}{n^r} E |\hat{g}_0 - E[\hat{g}_n \mid \mathcal{F}_{n-1}]|^{2r} \\ &\leq C \frac{1}{n^r} E \left| \sum_{l=0}^{n-1} E[(\hat{g}_l - E[\hat{g}_l \mid \mathcal{F}_{l-1}])^2 \mid \mathcal{F}_{l-1}] \right|^r + C \frac{1}{n^r} E[\hat{g}_0^{2r} + \hat{g}_n^{2r}] \\ &\leq C \frac{1}{n} \sum_{l=0}^n E \hat{g}_l^{2r} \leq C \sup_{0 \leq l \leq n} E \hat{g}_l^{2r} \leq CR^{2r} \sup_n E(V_n + 1)^{2r} < \infty \end{aligned}$$

by (A.11). Thus, (A.15) is now proved.

Next, we prove (iv). We prove (3.1) first. Fix $\mathbf{k} = (k_1, \dots, k_I)$ and $t \in \{1, \dots, T\}$. Let $\hat{g} = \hat{g}_{\mathbf{k}}^{(t)}$ be the solution to Poisson’s equation (A.19) which is a function of $\mathbf{\Lambda}$. Let $\mathbf{B}_{t,\mathbf{k}} \in \mathbf{L}(\Delta \mathcal{D})$ be the element whose value is $\mathbf{\Lambda}_n - \mathbf{\Lambda}_{n-1}$ with $D_n^{(t)}(\mathbf{k}) - D_{n-1}^{(t)}(\mathbf{k}) = 1 - \frac{1}{T}$, i.e., the $i(l, t)$ -th element of $\mathbf{B}_{t,\mathbf{k}}$ is

$$\left(\mathbb{I}_{t'=t} - \frac{1}{T}\right)w_o + \sum_{i=1}^n w_{m,i} \left(\mathbb{I}_{t'=t} - \frac{1}{T}\right)\mathbb{I}_{l_i=k_i} + w_s \left(\mathbb{I}_{t'=t} - \frac{1}{T}\right)\mathbb{I}_{l=\mathbf{k}}$$

for all strata \mathbf{l} and $t' = 1, \dots, T$. We show that (3.1) holds with

$$(\sigma^{(t)}(\mathbf{k}))^2 = \pi_\lambda[h_{\mathbf{k},\mathbf{k}}(t, \mathbf{\Lambda})],$$

where

$$\begin{aligned} h_{\mathbf{k},\mathbf{k}}(t, \mathbf{\Lambda}) &= \left(1 - \frac{2}{T}\right)p_{r_{n-1,t}(\mathbf{k})}p(\mathbf{k}) + \frac{1}{T^2}p(\mathbf{k}) + 2p^2(\mathbf{k})\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1} + \mathbf{B}_{t,\mathbf{k}})p_{r_{n-1,t}(\mathbf{k})} \\ &\quad - 2p^2(\mathbf{k})\frac{1}{T}\sum_{t'=1}^T\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1} + \mathbf{B}_{t',\mathbf{k}})p_{r_{n-1,t'}(\mathbf{k})}. \end{aligned}$$

Denote

$$\Delta M_{n,\mathbf{k}}^{(t)} = D_n^{(t)}(\mathbf{k}) - D_{n-1}^{(t)}(\mathbf{k}) + p(\mathbf{k})[\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n) - \widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1})]. \tag{A.20}$$

Then

$$\begin{aligned} \mathbb{E}[\Delta M_{n,\mathbf{k}}^{(t)} \mid \mathcal{F}_{n-1}] &= \mathbb{E}[D_n^{(t)}(\mathbf{k}) \mid \mathcal{F}_{n-1}] - D_{n-1}^{(t)}(\mathbf{k}) + p(\mathbf{k})[P_\lambda\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1}) - \widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1})] \\ &= \mathbb{E}[D_n^{(t)}(\mathbf{k}) \mid \mathcal{F}_{n-1}] - D_{n-1}^{(t)}(\mathbf{k}) - \bar{g}_{n-1,\mathbf{k}}^{(t)} \cdot p(\mathbf{k}) = 0 \end{aligned}$$

by (A.16) and (A.19). So, $\{\Delta M_{n,\mathbf{k}}^{(t)}\}$ is a sequence of martingale differences with

$$M_{n,\mathbf{k}}^{(t)} = \sum_{l=1}^n \Delta M_{l,\mathbf{k}}^{(t)} = D_n^{(t)}(\mathbf{k}) - D_0^{(t)}(\mathbf{k}) + p(\mathbf{k})[\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n) - \widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_0)] \tag{A.21}$$

and

$$\begin{aligned} \mathbb{E}[(\Delta M_{n,\mathbf{k}}^{(t)})^2 \mid \mathcal{F}_{n-1}] &= \mathbb{E}[(\Delta D_n^{(t)}(\mathbf{k}))^2 \mid \mathcal{F}_{n-1}] + p^2(\mathbf{k})\mathbb{E}[(\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n) - \widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1}))^2 \mid \mathcal{F}_{n-1}] \\ &\quad + 2p(\mathbf{k})\mathbb{E}[\Delta D_n^{(t)}(\mathbf{k})(\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n) - \widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1})) \mid \mathcal{F}_{n-1}] \\ &= \mathbb{E}[(\Delta D_n^{(t)}(\mathbf{k}))^2 \mid \mathcal{F}_{n-1}] - 2p^2(\mathbf{k})\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1})\{\mathbb{E}[\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n) \mid \mathcal{F}_{n-1}] - \widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1})\} \\ &\quad + p^2(\mathbf{k})\{\mathbb{E}[(\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n))^2 \mid \mathcal{F}_{n-1}] - (\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1}))^2\} \\ &\quad + 2p(\mathbf{k})\mathbb{E}[\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n)\Delta D_n^{(t)}(\mathbf{k}) \mid \mathcal{F}_{n-1}] - 2p(\mathbf{k})\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1})\mathbb{E}[\Delta D_n^{(t)}(\mathbf{k}) \mid \mathcal{F}_{n-1}] \\ &= h_{\mathbf{k},\mathbf{k}}(t, \mathbf{\Lambda}_{n-1}) + p^2(\mathbf{k})\{\mathbb{E}[(\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n))^2 \mid \mathcal{F}_{n-1}] - (\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_{n-1}))^2\}, \end{aligned}$$

where the last equality is due to the equation (A.19). It follows that

$$\mathbb{E}(M_{n,\mathbf{k}}^{(t)})^2 = \sum_{l=0}^{n-1} \mathbb{E}h_{\mathbf{k},\mathbf{k}}(t, \mathbf{\Lambda}_l) + p^2(\mathbf{k})\{\mathbb{E}(\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n))^2 - \mathbb{E}(\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_0))^2\}.$$

For $h_{\mathbf{k},\mathbf{k}}(t, \cdot)$, it is easily seen that $\pi_\lambda[h_{\mathbf{k},\mathbf{k}}(t, \cdot)] = (\sigma^{(t)}(\mathbf{k}))^2 \geq 0$ and

$$\begin{aligned} |h_{\mathbf{k},\mathbf{k}}(t, \mathbf{\Lambda})| &\leq 1 + 4 \sup_{t'} |\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda} + \mathbf{B}_{t',\mathbf{k}})| \\ &\leq 1 + 4R \sup_{t'} (V(\mathbf{\Lambda} + \mathbf{B}_{t',\mathbf{k}}) + 1) \leq c_0(V(\mathbf{\Lambda}) + 1), \end{aligned}$$

where c_0 is a constant. By (A.10) (with $r = 1$) and applying [26, Theorem 17.4.2] again, we have a function $\widehat{h}(t, \mathbf{\Lambda})$ such that

$$\widehat{h} - P_\lambda\widehat{h} = h_{\mathbf{k},\mathbf{k}}(t, \mathbf{\Lambda}) - \pi_\lambda[h_{\mathbf{k},\mathbf{k}}(t, \mathbf{\Lambda})] \quad \text{and} \quad |\widehat{h}| \leq c(V^2 + 1).$$

It follows that

$$\mathbb{E}[(M_{n,\mathbf{k}}^{(t)})^2] = \sum_{l=0}^{n-1} \pi_\lambda[h_{\mathbf{k},\mathbf{k}}(t, \mathbf{\Lambda}_l)] + \sum_{l=0}^{n-1} \mathbb{E}\{\widehat{h}(t, \mathbf{\Lambda}_l) - P_\lambda\widehat{h}(t, \mathbf{\Lambda}_l)\} + p^2(\mathbf{k})\{\mathbb{E}(\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n))^2 - \mathbb{E}(\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_0))^2\}$$

$$\begin{aligned} &= n(\sigma^{(t)}(\mathbf{k}))^2 + \{E\widehat{h}(t, \mathbf{\Lambda}_0) - E\widehat{h}(t, \mathbf{\Lambda}_n)\} + p^2(\mathbf{k})\{E(\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n))^2 - E(\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_0))^2\} \\ &= n(\sigma^{(t)}(\mathbf{k}))^2 + O(1) \end{aligned} \tag{A.22}$$

by (A.11) (with $r = 2$); notice that $EV^2(\mathbf{\Lambda}_n)$ is bounded. Hence, (3.1) is proved.

Notice

$$E|\Delta M_{n,\mathbf{k}}^{(t)}|^r \leq c + c \sup_n E|\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n)|^r \leq c + c \sup_n EV^r(\mathbf{\Lambda}_n) < \infty$$

by (A.11). By the central limit theorem for martingales, we conclude that

$$\frac{D_n^{(t)}(\mathbf{k})}{\sqrt{n}} = \frac{M_{n,\mathbf{k}}^{(t)} + O_P(1)}{\sqrt{n}} \xrightarrow{d} N(0, (\sigma^{(t)}(\mathbf{k}))^2).$$

The asymptotic normality (3.2) is proved. The asymptotic normality together with (A.15) implies (3.3). The proof of (iv) is completed.

For (v) and (vi), notice that if $D_n^{(t)}(\mathbf{k}) = o_P(\sqrt{n})$, then $D_n^{(t)}(\mathbf{k}) = o(\sqrt{n})$ in L_2 by (A.15). So $\sigma^{(t)}(\mathbf{k}) = 0$. Hence,

$$E(D_n^{(t)}(\mathbf{k}))^2 = O(1)$$

by (3.1). (v) is proved.

Furthermore,

$$E[M_{n,\mathbf{k}}^{(t)}]^2 = O(1)$$

by (A.22). By the martingale convergence theorem, there is a random variable $M_\infty^{(t)}$ such that

$$M_{n,\mathbf{k}}^{(t)} \rightarrow M_\infty^{(t)} \quad \text{a.s.} \quad \text{and} \quad M_{n,\mathbf{k}}^{(t)} = E[M_\infty^{(t)} | \mathcal{F}_n]. \tag{A.23}$$

On the other hand, the sequence $((D_n^{(t)}(\mathbf{k}), \mathbf{\Lambda}_n))_{n \geq 1}$ is an irreducible Markov chain by (A.8). Hence, it is a positive (Harris) recurrent Markov chain by [26, Proposition 18.3.1] due to the fact that it is bounded in probability. Recall the equation (A.21). The left-hand side is a martingale which is convergent almost surely due to (A.23), while the right-hand side is a function of a positive (Harris) recurrent Markov chain. It follows that the limit $M_\infty^{(t)}$ must be a constant. So

$$M_{n,\mathbf{k}}^{(t)} = E[M_\infty^{(t)} | \mathcal{F}_n] = \text{const.} \quad \text{a.s.}$$

It is obvious from (A.21) that $M_0^{(t)} = 0$. Hence $M_{n,\mathbf{k}}^{(t)} \equiv 0$ a.s. It follows that

$$D_n^{(t)}(\mathbf{k}) = D_0^{(t)}(\mathbf{k}) - p(\mathbf{k})[\widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_n) - \widehat{g}_{\mathbf{k}}^{(t)}(\mathbf{\Lambda}_0)], \tag{A.24}$$

which implies that $D^{(t)}(\mathbf{k})$ is a function of $\mathbf{\Lambda}$. Up to now, we arrive at the conclusion that if

$$D_n^{(t)}(\mathbf{k}) = o_P(\sqrt{n}),$$

then $D^{(t)}(\mathbf{k})$ is a function of $\mathbf{\Lambda}$.

Finally, we show that we will get a contradiction in (A.24) when $w_s = 0$. Recall that for any fixed $t \in \{1, \dots, T\}$ and \mathbf{k} , $\mathbf{B}_{t,\mathbf{k}}$ is the value of $\mathbf{\Lambda}_n - \mathbf{\Lambda}_{n-1}$ with $\Delta D_n^{(t)}(\mathbf{k}) = 1 - \frac{1}{T}$. We write the $i(\mathbf{l}, t')$ -th element of $\mathbf{B}_{t,\mathbf{k}}$ as $\mathbf{B}_{t,\mathbf{k}}(\mathbf{l}, t')$, and

$$\mathbf{B}_{t,\mathbf{k}}(\mathbf{l}, t') = w_o \left(\mathbb{I}_{t'=t} - \frac{1}{T} \right) + \sum_{i=1}^I w_{m,i} \left(\mathbb{I}_{t'=t} - \frac{1}{T} \right) \cdot \mathbb{I}_{l_i=k_i}.$$

Choose a stratum \mathbf{k}^* such that $k_i^* \neq k_i$ ($1 \leq i \leq I$). It follows that

$$\sum_{i=1}^{T-1} [\mathbf{B}_{\bar{i},\mathbf{k}}(\mathbf{l}, t') + \mathbf{B}_{\bar{i},\mathbf{k}^*}(\mathbf{l}, t')] + \mathbf{B}_{T,(k_1^*,k_2^*,\dots,k_I)}(\mathbf{l}, t') + \mathbf{B}_{T,(k_1,k_2^*,\dots,k_I^*)}(\mathbf{l}, t')$$

$$= w_o \left[\sum_{\bar{t}=1}^T \mathbb{I}_{t'=\bar{t}} - 1 \right] + \sum_{i=1}^I w_{m,i} \left[\sum_{\bar{t}=1}^T \mathbb{I}_{t'=\bar{t}} - 1 \right] \cdot \mathbb{I}_{(l_i=k_i \text{ or } k_i^*)} = 0,$$

i.e.,

$$\sum_{\bar{t}=1}^{T-1} [\mathbf{B}_{\bar{t},\mathbf{k}} + \mathbf{B}_{\bar{t},\mathbf{k}^*}] + \mathbf{B}_{T,(k_1^*,k_2,\dots,k_I)} + \mathbf{B}_{T,(k_1,k_2^*,\dots,k_I^*)} = \mathbf{0},$$

where $\mathbf{0} \in \mathbb{R}^{T \times m}$ and all the values are 0. Define

$$\Delta N_n^{(t)}(\mathbf{k}) = N_n^{(t)}(\mathbf{k}) - N_{n-1}^{(t)}(\mathbf{k}).$$

It follows that on the event

$$E = \{ \Delta N_{n+2(\bar{t}-1)}^{(\bar{t})}(\mathbf{k}) = 1, \Delta N_{n+2\bar{t}-1}^{(\bar{t})}(\mathbf{k}^*) = 1, \bar{t} = 1, \dots, T-1, \\ \Delta N_{n+2(T-1)}^{(T)}(k_1^*, k_2, \dots, k_I) = 1, \Delta N_{n+2T-1}^{(T)}(k_1, k_2^*, \dots, k_I^*) = 1 \},$$

the value of Λ does not change, so the value of the right-hand side of (A.24) does not change, i.e.,

$$-p(\mathbf{k})[\widehat{g}_{\mathbf{k}}^{(t)}(\Lambda_{n+2T-1}) - \widehat{g}_{\mathbf{k}}^{(t)}(\Lambda_{n-1})] = 0.$$

However, on the event E ,

$$D_{n+2T-1}^{(t)}(\mathbf{k}) - D_{n-1}^{(t)}(\mathbf{k}) = \frac{1}{T}.$$

On the other hand, it is easily seen that conditional on \mathbf{D}_{n-1} , the probability of E is positive. We obtain a contradiction to (A.24). The proof of Theorem 3.3 is now completed. \square

Proof of Theorem 3.6. Define

$$h_{\mathbf{k},\mathbf{l}}(t, \Lambda) = p(\mathbf{k})\mathbb{E}[\Delta D_n^{(t)}(\mathbf{l})\widehat{g}_{\mathbf{k}}^{(t)}(\Lambda_n) \mid \mathcal{F}_{n-1}] + p(\mathbf{l})\mathbb{E}[\Delta D_n^{(t)}(\mathbf{k})\widehat{g}_{\mathbf{l}}^{(t)}(\Lambda_n) \mid \mathcal{F}_{n-1}].$$

For the martingale difference in (A.20), by (A.19) we can also show that

$$\mathbb{E}[\Delta M_{n,\mathbf{k}}^{(t)} \Delta M_{n,\mathbf{l}}^{(t)} \mid \mathcal{F}_{n-1}] \\ = p(\mathbf{k})\mathbb{E}[\Delta D_n^{(t)}(\mathbf{l})\widehat{g}_{\mathbf{k}}^{(t)}(\Lambda_n) \mid \mathcal{F}_{n-1}] + p(\mathbf{l})\mathbb{E}[\Delta D_n^{(t)}(\mathbf{k})\widehat{g}_{\mathbf{l}}^{(t)}(\Lambda_{n-1}) \mid \mathcal{F}_{n-1}] \\ + p(\mathbf{k})p(\mathbf{l})[\mathbb{E}[\widehat{g}_{\mathbf{k}}^{(t)}(\Lambda_n)\widehat{g}_{\mathbf{l}}^{(t)}(\Lambda_n) \mid \mathcal{F}_{n-1}] - \widehat{g}_{\mathbf{k}}^{(t)}(\Lambda_{n-1})\widehat{g}_{\mathbf{l}}^{(t)}(\Lambda_{n-1})] \\ = h_{\mathbf{k},\mathbf{l}}(t, \Lambda_{n-1}) + p(\mathbf{k})p(\mathbf{l})[\mathbb{E}[\widehat{g}_{\mathbf{k}}^{(t)}(\Lambda_n)\widehat{g}_{\mathbf{l}}^{(t)}(\Lambda_n) \mid \mathcal{F}_{n-1}] - \widehat{g}_{\mathbf{k}}^{(t)}(\Lambda_{n-1})\widehat{g}_{\mathbf{l}}^{(t)}(\Lambda_{n-1})]$$

for $\mathbf{k} \neq \mathbf{l}$. We know that $|h_{\mathbf{k},\mathbf{l}}(t, \Lambda)|$ is bounded by $c_2(V(\Lambda) + 1)$. With the same argument as that for obtaining (A.22), we have

$$\mathbb{E}[M_{n,\mathbf{k}}^{(t)} M_{n,\mathbf{l}}^{(t)}] = \sum_{l=1}^n \mathbb{E}[\Delta M_{l,\mathbf{k}} \Delta M_{l,\mathbf{l}}^{(t)}] = n\pi[h_{\mathbf{k},\mathbf{l}}] + O(1).$$

Define

$$M_n(i; k_i)^{(t)} = \sum_{\mathbf{k} \setminus k_i} M_{n,\mathbf{k}}^{(t)}.$$

It follows that

$$\mathbb{E}[(M_n^{(t)}(i; k_i))^2] = n(\sigma^{(t)}(i; k_i))^2 + O(1).$$

Taking summation on both sides of (A.21) over $\mathbf{k} \setminus k_i$ yields

$$M_n^{(t)}(i; k_i) = D_n^{(t)}(i; k_i) - D_0^{(t)}(i; k_i) + g_{i;k_i}^{(t)}(\Lambda_n),$$

where

$$g_{i;k_i}^{(t)}(\Lambda_n) = \sum_{\mathbf{k} \setminus k_i} p(\mathbf{k})[\widehat{g}_{\mathbf{k}}^{(t)}(\Lambda_n) - \widehat{g}_{\mathbf{k}}^{(t)}(\Lambda_0)]$$

is a function of $\mathbf{\Lambda}_n$. Hence,

$$E[(D_n^{(t)}(i; k_i))^2] = n(\sigma^{(t)}(i; k_i))^2 + O(\sqrt{n}\sigma^{(t)}(i; k_i)). \quad (\text{A.25})$$

With the same argument as that for obtaining (A.24), if $\sigma^{(t)}(i; k_i) = 0$, then we have

$$M_n^{(t)}(i; k_i) \equiv 0$$

and

$$D_n^{(t)}(i; k_i) - D_0^{(t)}(i; k_i) = -g_{i; k_i}^{(t)}(\mathbf{\Lambda}_n). \quad (\text{A.26})$$

Under the condition $w_s + w_{m,i} = 0$, $\mathbf{\Lambda}_n$ is a linear transformation of $(D_n^{(t)}(j; k_j) : j = 1, \dots, i-1, i+1, \dots, I, k_j = 1, \dots, m_j)$ which excludes the values of marginal imbalances $D^{(t)}(i; l_i)$ ($l_i = 1, \dots, m_i$) of the i -th covariate. It follows that for $\Delta N_n^{(t)}(\mathbf{k}) = 1$ and $\Delta N_n^{(t)}(k_1, \dots, k_{i-1}, k_i^*, k_{i+1}, \dots, k_I) = 1$, $\Delta \mathbf{\Lambda}_n$ is the same, so the values changed on the right-hand side of (A.26) are the same. Obviously, the values changed on the left-hand side of (A.26) are different, one of which is $1 - \frac{1}{I}$, and the other is 0. We obtain a contradiction. \square